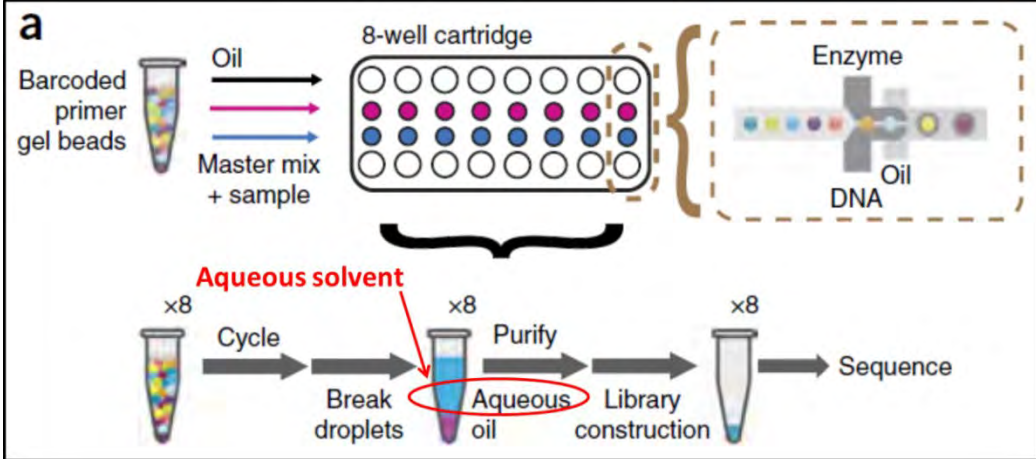
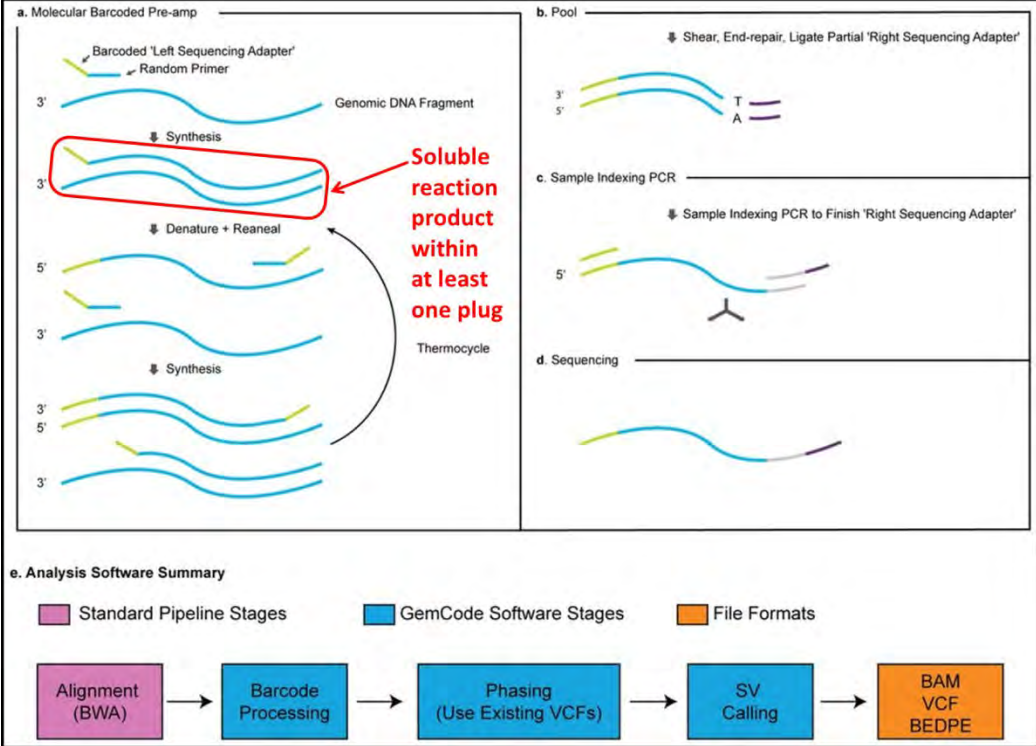
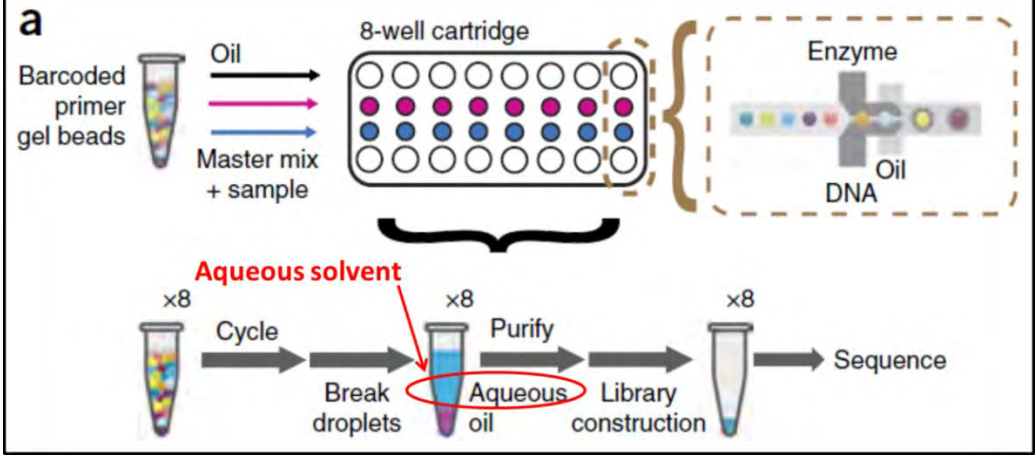


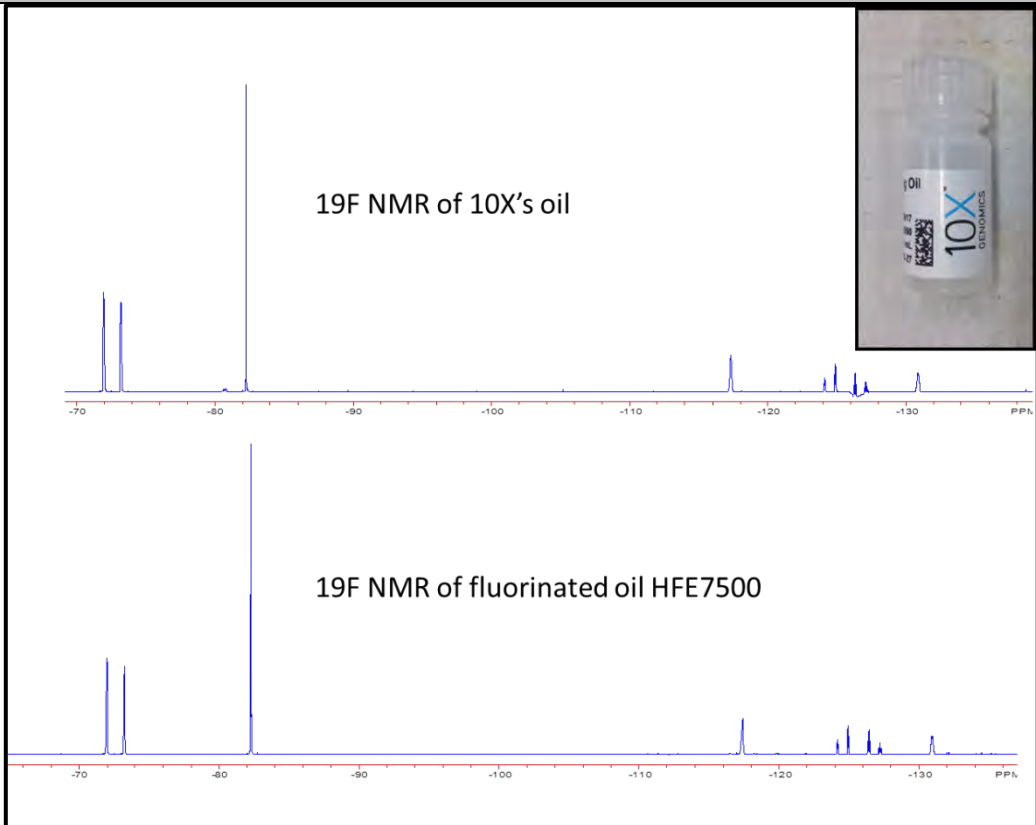
	'091 Claim Language	Infringement Support
		<p>channels. As a result, the plugs contain a solvent (water).</p>  <p>Ex. 5 [<i>Nature Biotechnology</i>] at Fig. 1a.</p>
091-11	11. The method of claim 1, wherein the reaction of the plug-fluids forms a soluble reaction product within at least one plug.	<p><b><u>10X's GemCode platform forms a DNA amplification product, which is soluble within the aqueous plug fluid.</u></b></p> <ul style="list-style-type: none"> <li>The DNA amplification process which occurs in the microfluidic droplets of 10X's GemCode platform is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp." This figure is taken from 10X's recent article in <i>Nature Biotechnology</i>, which presents data based on the use of 10X's GemCode platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

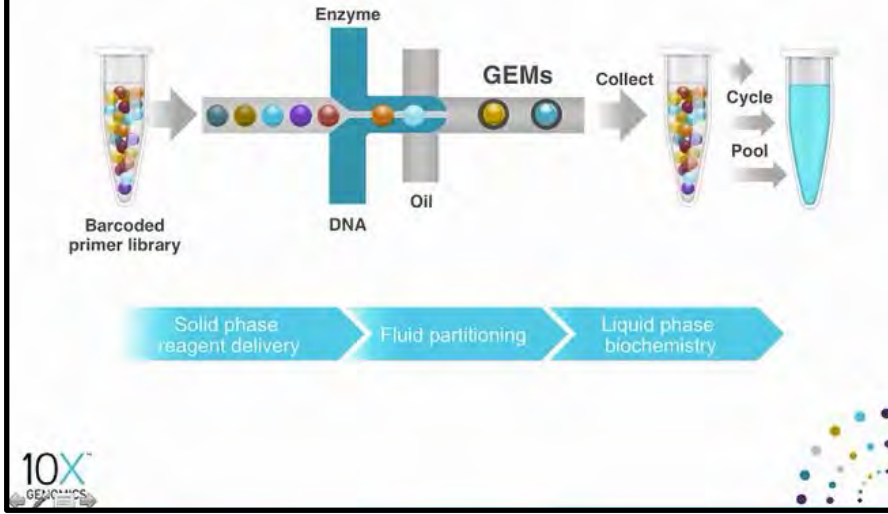
	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the 10X Genomics sequencing workflow. Stage (a) shows the Molecular Barcoded Pre-amp process where genomic DNA fragments are amplified using a barcoded left sequencing adapter and a random primer. Stage (b) shows the Pooling step where DNA is sheared, end-repaired, and ligated with a partial right sequencing adapter. Stage (c) shows Sample Indexing PCR to finish the right sequencing adapter. Stage (d) shows the final Sequencing step. Stage (e) is the Analysis Software Summary, showing a flow from Alignment (BWA) to Barcode Processing, Phasing (Use Existing VCFs), SV Calling, and finally to BAM, VCF, and BEDPE file formats. A red box highlights the pre-amplification step (a) with a red arrow pointing to it and the text "Soluble reaction product within at least one plug".</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b>amplify the DNA</b> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432. The DNA amplification product is soluble in water.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schnall-Levin described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can</li> </ul>

	'091 Claim Language	Infringement Support
		<p>concentrate on the top panel showing the biochemistry that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 5 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 579 1659 1237" data-label="Diagram"> <p>The diagram illustrates the process of low-input molecular barcoding in GEMs. It consists of four main steps:</p> <ol style="list-style-type: none"> <li><b>1 Molecular barcoding in GEMs</b>: This step shows DNA molecules (blue lines) with barcodes (yellow and blue segments) being amplified. A red arrow points to the 'Soluble reaction product'.</li> <li><b>2 Pool, Ligate right adapter</b>: This step involves shearing, end-repair, A-tailing, and ligation of the DNA molecules.</li> <li><b>3 Sample Indexing PCR</b>: This step shows the DNA molecules being amplified with a specific primer.</li> <li><b>4 Sequence and Analyze</b>: This step shows the final DNA molecules being sequenced and analyzed.</li> </ol> <p>The diagram also includes a 'Cycle' icon and a small cluster of colored dots in the bottom right corner.</p> </div> <ul style="list-style-type: none"> <li>• The amplified DNA product is soluble in the aqueous droplets.</li> </ul>

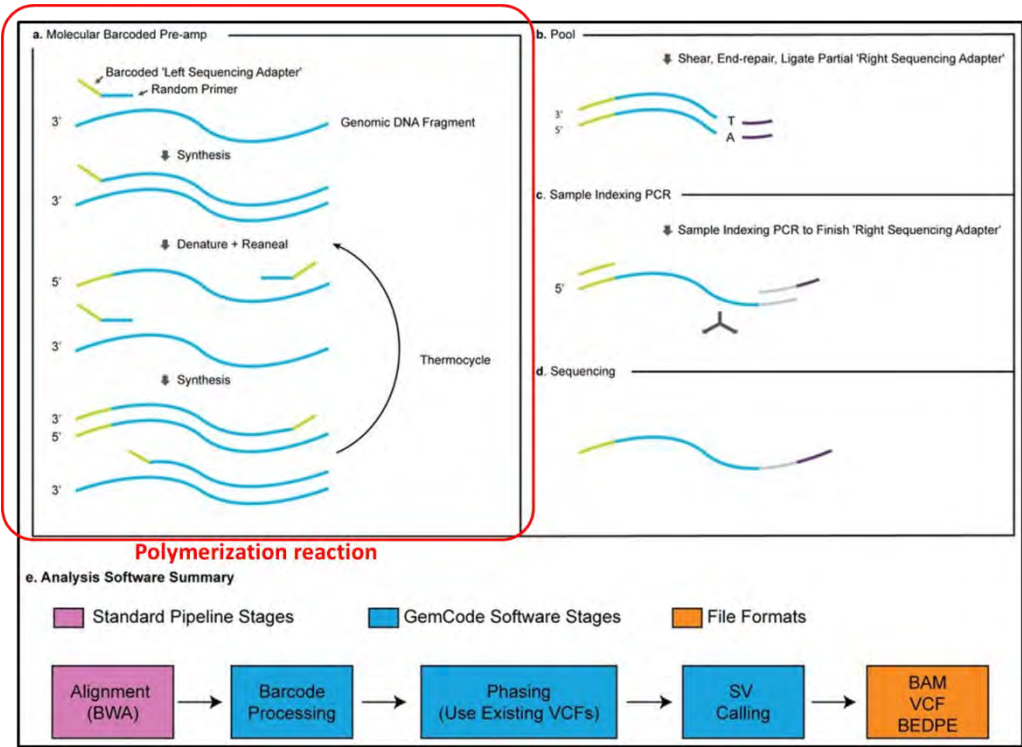
	'091 Claim Language	Infringement Support
091-23	23. The method of claim 1, further comprising detecting the product of the reaction.	<p><b><u>The product of the DNA amplification reaction is detected by DNA sequencing.</u></b></p> <ul style="list-style-type: none"> <li>The DNA that results from the amplification reaction in 10X's product includes additional specialized DNA sequences so that the amplified DNA can be sequenced, and hence detected, on an Illumina DNA sequencing instrument. As 10X explained in its recent <i>Nature Biotechnology</i> paper, "[t]o create barcoded DNA molecules for sequencing, we perform an optimized droplet-based assay that introduces a barcode-containing sequencing adapter into new fragments (Online Methods). HMW DNA templates, ranging from ten to several hundred kilobases in size, are randomly distributed in picoliter reaction volumes across &gt;100,000 droplets. Within an individual droplet, gel bead dissolution releases the amplification primer into the partitioned solution. The primer contains the following components: (i) an Illumina P5 flow cell primer sequence, (ii) a 14-bp barcode, (iii) an Illumina R1 sequence (read 1 sequencing primer) and (iv) a 10-bp random primer sequence (Supplementary Fig. 1)." Ex. 5 [Nature Biotechnology] at 2.</li> </ul>
091-27	27. The method of claim 1, wherein refractive indices of the carrier-fluid and the plug-fluids are substantially similar.	<p>10X's GemCode platform performs "the method of claim 1, wherein refractive indices of the carrier-fluid and the plug-fluids are substantially similar."</p> <ul style="list-style-type: none"> <li>The plug fluid is aqueous.</li> <li>The carrier fluid is a fluorinated oil comprised primarily of HFE7500.</li> <li>Water and fluorinated oil have substantially similar refractive indices.</li> </ul> <p><b><u>10X's GemCode platform uses aqueous plug fluids.</u></b></p> <ul style="list-style-type: none"> <li>The droplets that are formed in 10X's microfluidic device are broken after a DNA amplification reaction is carried out inside the droplet. The fluid that is inside the droplets separates from the oil that originally surrounded and carried the droplets. As depicted below, the interior of the droplet is "Aqueous" and is shown in blue. Thus, the channels that provided the fluids for the interior of the droplets are aqueous fluid channels.</li> </ul>

	'091 Claim Language	Infringement Support
		<p><b>a</b></p>  <p>Oil</p> <p>Master mix + sample</p> <p>8-well cartridge</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>Aqueous solvent</p> <p>x8</p> <p>Cycle</p> <p>Break droplets</p> <p>x8</p> <p>Purify</p> <p>Aqueous</p> <p>oil</p> <p>Library construction</p> <p>x8</p> <p>Sequence</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Fig. 1a.</p> <p><b><u>10X's GemCode platform uses a fluorinated oil carrier fluid with a refractive index substantially similar to water.</u></b></p> <ul style="list-style-type: none"> <li>A comparison of the <math>^{19}\text{F}</math> nuclear magnetic resonance spectrum for 10X's partitioning oil (i.e., carrier fluid) to the spectrum for the commercially available fluorinated oil HFE7500 reveals that 10X's partitioning oil consists primarily of HFE7500. HFE7500 has a refractive index of 1.29 and water has a refractive index of 1.333. The refractive index of the carrier fluid and plug fluid are thus substantially similar.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>19F NMR of 10X's oil</p> <p>19F NMR of fluorinated oil HFE7500</p>
091-29	29. The method of claim 1, further comprising employing a number of devices in parallel.	<p><b><u>10X's GemCode platform uses microfluidic chips with eight channels in parallel allowing for eight samples to be tested in parallel.</u></b></p> <ul style="list-style-type: none"> <li>As Dr. Schnall Levin explained during his August 2015 webinar, below is a "cross-section of one of the channels present in [10X's] microfluidic chip. <i>If you look at one of our microfluidic chips there would be eight of these channels in parallel such that you can run eight samples at a time.</i>" Ex. 4 [10X Webinar] at 9:32-47.</li> </ul>

	'091 Claim Language	Infringement Support
		<p data-bbox="840 308 1512 349">&gt;100,000 Reactions Assembled in &lt; 5 min</p> 
091-31	31. The method of claim 1, wherein the reaction is a polymerization reaction.	<p data-bbox="693 1079 1869 1144"><b><u>10X's GemCode platform conducts a polymerization reaction in droplets so that it can amplify DNA.</u></b></p> <ul data-bbox="735 1185 1879 1372" style="list-style-type: none"> <li>• Polymerase chain reaction ("PCR") involves the use of an extension enzyme, DNA primers, and nucleotides to amplify DNA. The process takes place through a cycling protocol in which DNA is denatured into single strands, and then replicated by an enzyme in a polymerization reaction. The DNA product of this reaction cycle is then used as the starting material for the next round of amplification.</li> </ul>

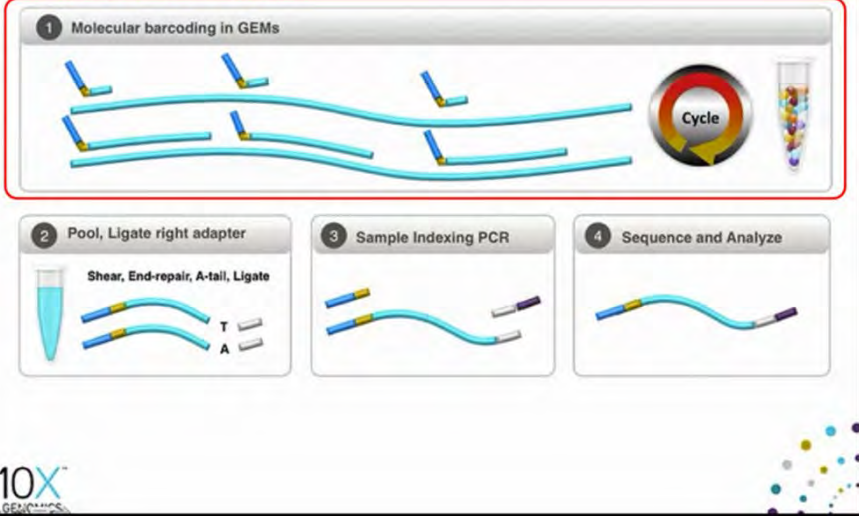


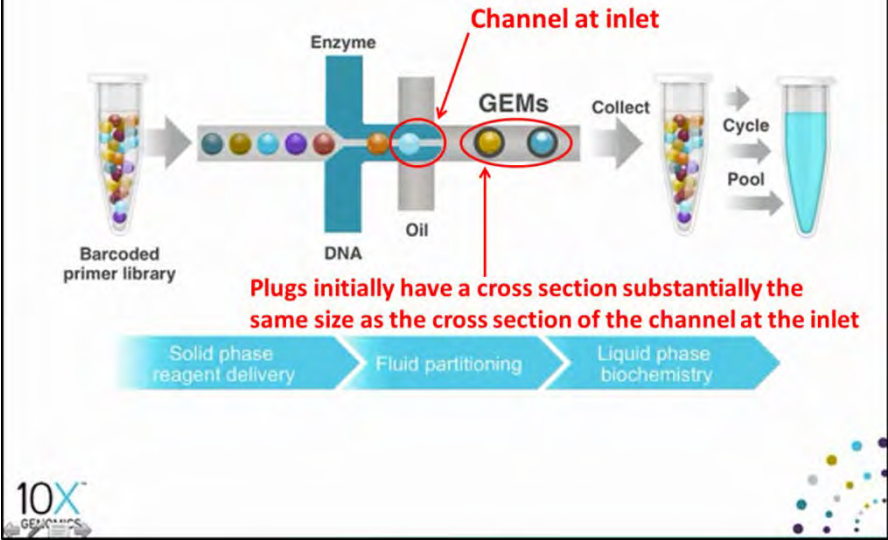
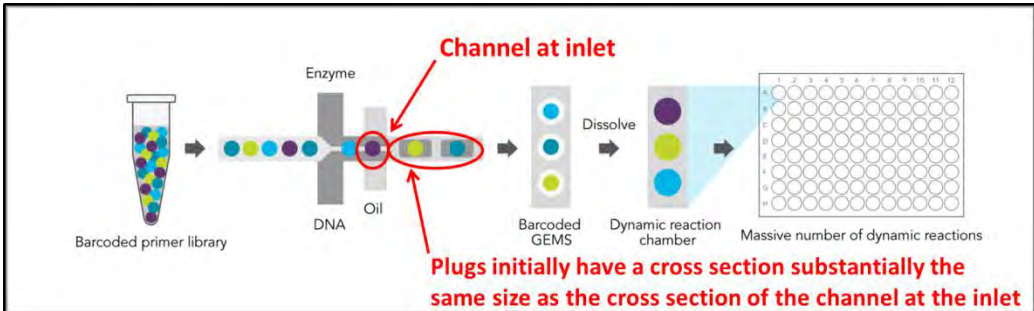
	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li> <p>This process is depicted in the figure below in the panel labeled “a. Molecular Barcoded Pre-amp.” This figure is taken from 10X’s recent article in <i>Nature Biotechnology</i>, which presents data based on the use of 10X’s GemCode platform. The figure below shows a single stranded “Genomic DNA Fragment” that is extended through the use of a “Random Primer.” The extension that takes place is a polymerization reaction. The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</p> </li> </ul>  <p><b>Polymerization reaction</b></p> <p><b>e. Analysis Software Summary</b></p> <p>Standard Pipeline Stages      GemCode Software Stages      File Formats</p> <pre> graph LR     A[Alignment BWA] --&gt; B[Barcode Processing]     B --&gt; C[Phasing Use Existing VCFs]     C --&gt; D[SV Calling]     D --&gt; E[BAM VCF BEDPE]   </pre>

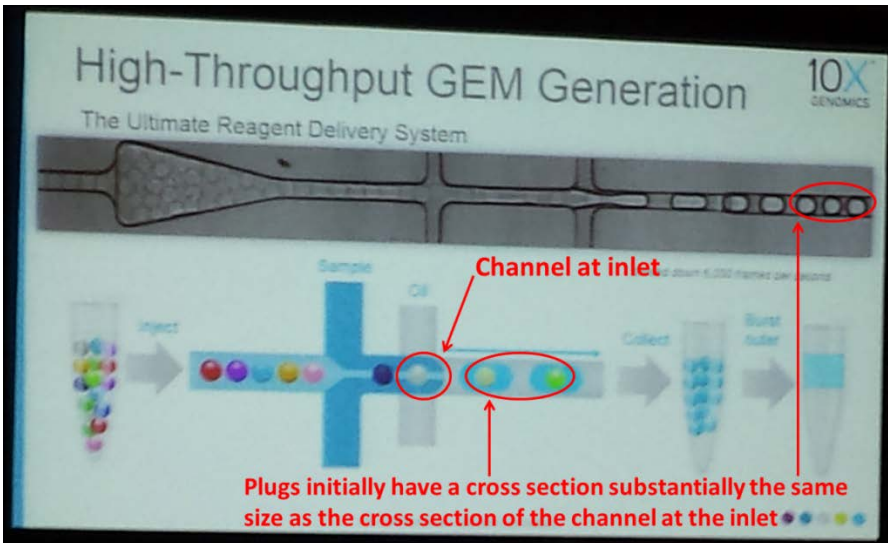
Ex. 5 [*Nature Biotechnology*] at Supp. Fig. 1. As 10X’s publication states, “1 ng of

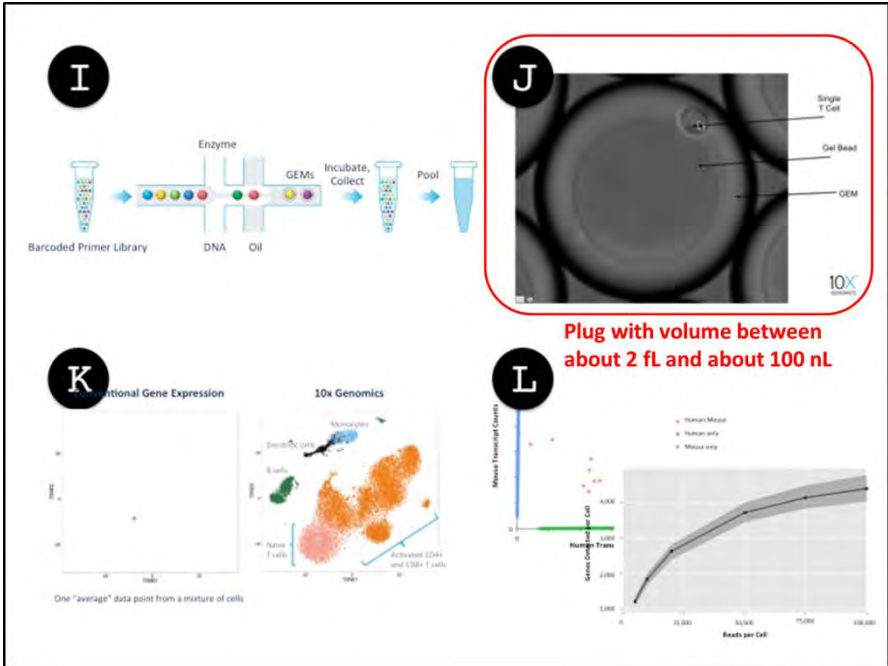


	'091 Claim Language	Infringement Support
		<p>sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b><i>amplify the DNA</i></b> and introduce 14-bp partition barcodes.” <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schnall-Levin described the DNA amplification reaction, which includes a polymerization reaction, that takes place in the droplets with reference to the figure below. “So now the biochemistry that’s happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you’ve broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry that’s happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</li> </ul>

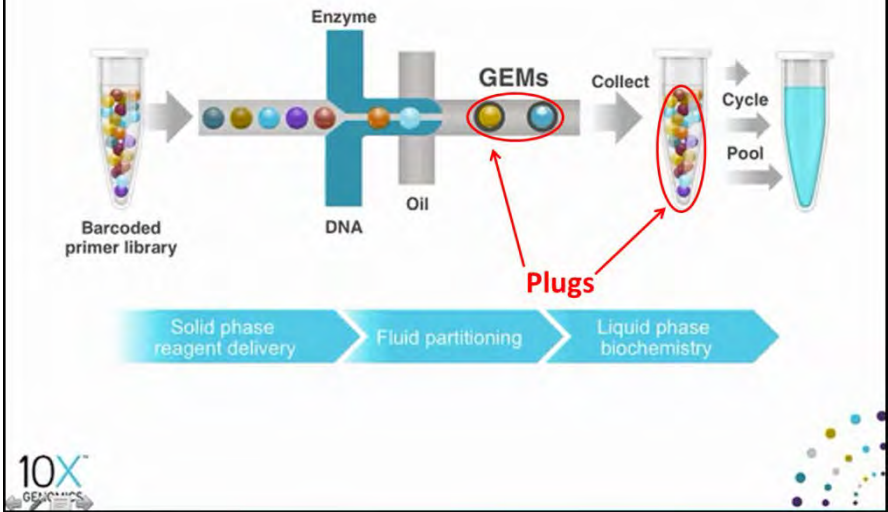
	'091 Claim Language	Infringement Support
		<p data-bbox="848 305 1482 344">Low-input Molecular Barcoding in GEMs</p> <p data-bbox="842 370 1119 396"><b>Polymerization reaction</b></p> 
091-33	33. The method of claim 1, wherein each plug initially has a cross section that is substantially the same size as the cross section of the channel at the inlet.	<p data-bbox="695 993 1881 1097"><b><u>The microfluidic droplets in 10X's GemCode platform initially have a cross section that is substantially the same size as the cross section of the channel containing the aqueous fluids.</u></b></p> <ul data-bbox="743 1143 1881 1286" style="list-style-type: none"> <li>During his August webinar, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the <i>channel in our microfluidic chip</i>.” <i>Id.</i> at 9:33-39. In that picture, each plug labeled GEMs has a cross section substantially the same size as the cross section as the cross section of the center channel.</li> </ul>

	'091 Claim Language	Infringement Support
		<p data-bbox="835 305 1514 345">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p data-bbox="1031 662 1644 727"><b>Plugs initially have a cross section substantially the same size as the cross section of the channel at the inlet</b></p> <p data-bbox="741 971 1892 1044">• 10x's website is also consistent in showing that the cross section of the plug is initially substantially the same size as the cross section of the center channel.</p>  <p data-bbox="1220 1328 1812 1385"><b>Plugs initially have a cross section substantially the same size as the cross section of the channel at the inlet</b></p>

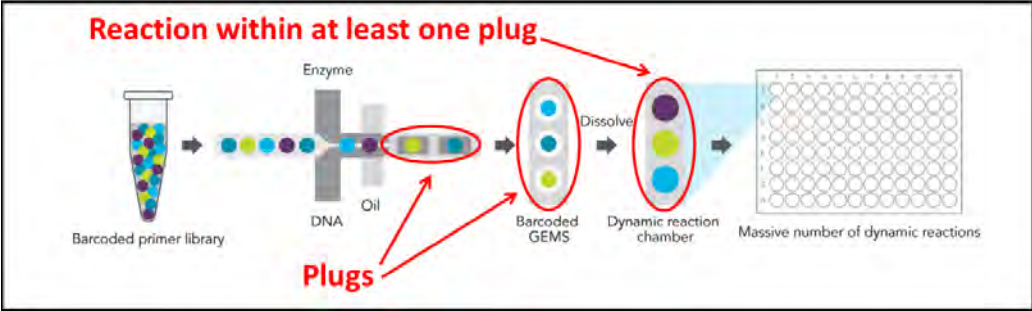
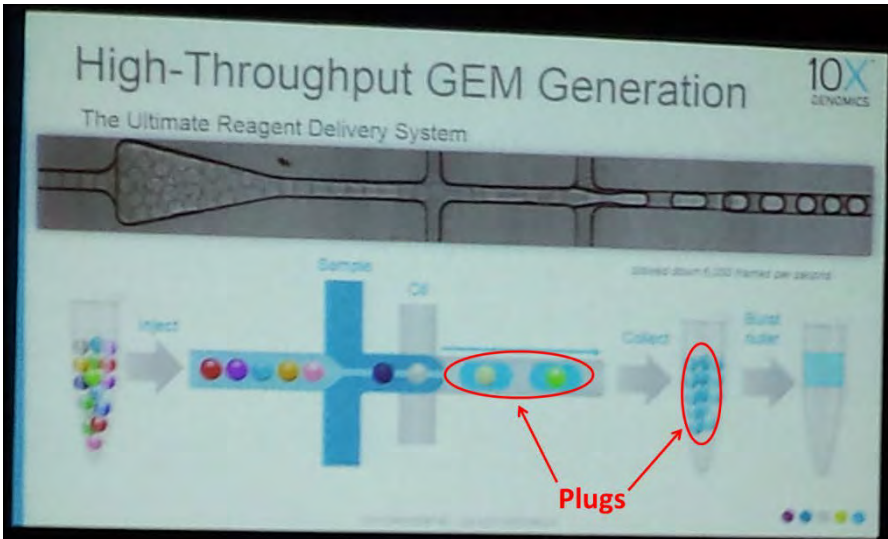
	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles and initially have a cross section that is substantially the same as the cross section of the center channel.</li> </ul>  <p>Ex. 37 [JP Morgan presentation] at 2.</p>
091-35	35. The method of claim 1, wherein the volume of at least one plug is about 1 femtoliter to about 250 nL.	<p><b><u>10X's droplets have a volume between 1 femtoliters and about 250 nanoliters.</u></b></p> <ul style="list-style-type: none"> <li>At the 2016 AGBT conference, 10X provided a workshop in which it described its technology. The figure below from 10X's workshop presentation depicts in Panel J a droplet alongside a "Single T Cell." Based on the fact that a T cell is roughly 10 <math>\mu\text{m}</math> in</li> </ul>

	'091 Claim Language	Infringement Support
		<p>diameter, 10X's droplets are roughly 100 <math>\mu\text{m}</math> in diameter. This leads to a droplet volume in 10X's GemCode platform of roughly 0.5 nanoliters, which is between two femtoliters and one hundred nanoliters.</p>  <p>Ex. 40 [Core Genomics Summary] at ____.</p>
091-36a	36. A method of conducting a reaction within at least one plug comprising the steps of:	<p>10X's GemCode platform uses "method of conducting a reaction within at least one plug."</p> <ul style="list-style-type: none"> <li>• The plugs are microfluidic droplets that are formed in 10X's GemCode platform.</li> <li>• A reaction that is conducted in the plug is a DNA amplification reaction.</li> </ul> <p><b><u>10X's GemCode platform is a microfluidic system using "plugs," which 10X refers to as</u></b></p>

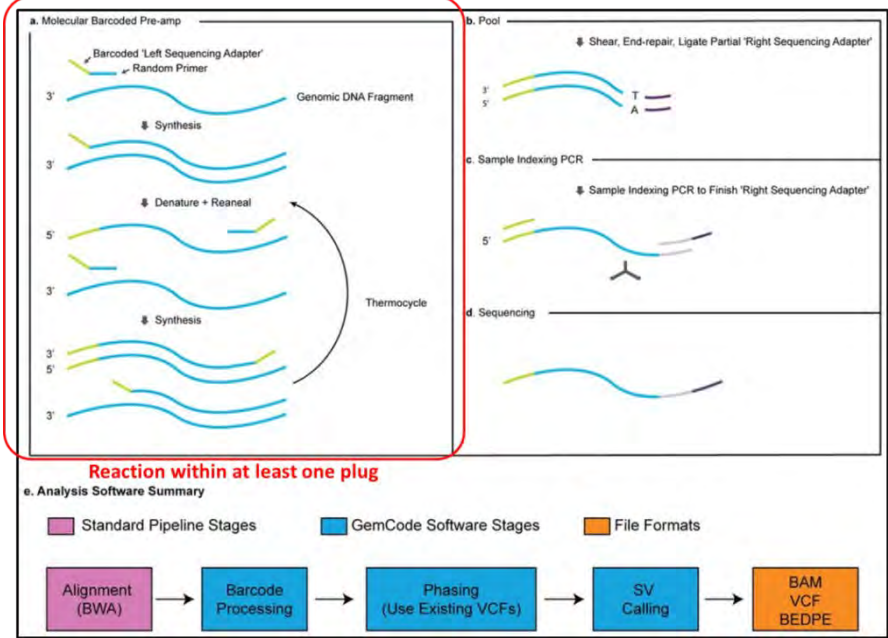
	'091 Claim Language	Infringement Support
		<p><b><u>droplets or “GEMs”</u></b></p> <ul style="list-style-type: none"> <li>• The '091 patent's description of “plugs” includes the following: “‘Plugs’ in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible.” Ex. 11 ['091 patent] at 9:20-23.</li> <li>• On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar “about the GemCode platform.” Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 (“I’m really excited today to take you through our Platform.”). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '091 patent with reference to the below figure: “If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>” <i>Id.</i> at 9:48-10:39.</li> </ul>

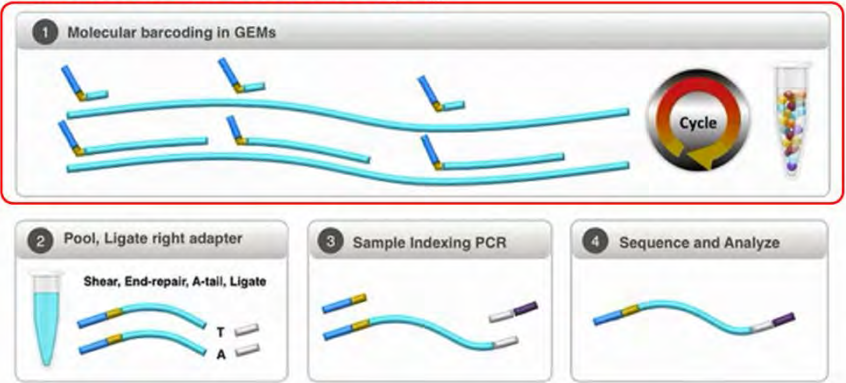
	'091 Claim Language	Infringement Support
		<p data-bbox="835 305 1514 345">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <ul style="list-style-type: none"> <li data-bbox="741 971 1896 1149">10x's website is consistent with Dr. Schnall-Levin's description of 10X's Platform. 10X's website states that "[t]he instrument features precise <i>microfluidics</i> coupled with single button, user-friendly operation." Ex. 39 [10X Website Excerpts] at 1. The website further states that the 10X chip kit "[c]ontains the <i>microfluidic chips</i> and accessories required for sample partitioning." <i>Id.</i> at 5.</li> </ul>

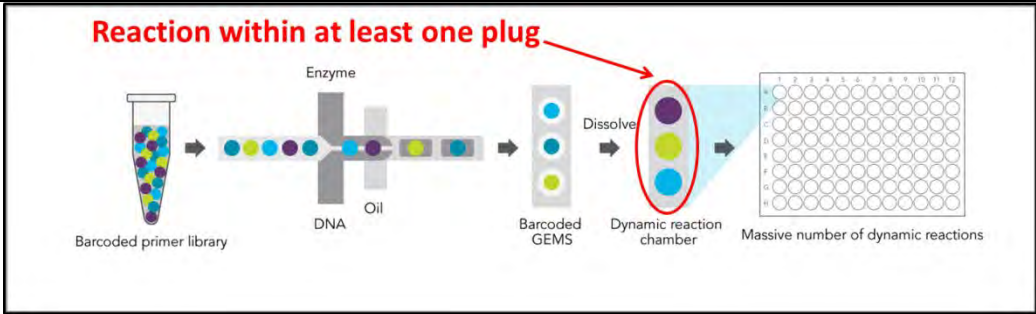


	'091 Claim Language	Infringement Support
		 <p><b>Reaction within at least one plug</b></p> <p>Barcoded primer library → Enzyme → DNA → Oil → Plugs → Dissolve → Dynamic reaction chamber → Massive number of dynamic reactions</p> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul>  <p>High-Throughput GEM Generation The Ultimate Reagent Delivery System 10X GENOMICS</p> <p>Inject → Sample → Oil → Collect → Burst outlet</p> <p>Plugs</p>

	'091 Claim Language	Infringement Support
		<p>Ex. 37 [JP Morgan presentation] at 2.</p> <p><b><u>10X's GemCode platform conducts DNA amplification reactions within the microfluidic droplets ("plugs")</u></b></p> <ul style="list-style-type: none"> <li>• The slide above from 10X's August 2015 presentation is entitled "&gt;100,000 <i>Reactions</i> Assembled in &lt;5 min," which demonstrates that reactions are occurring within the microfluidic droplets.</li> <li>• The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp," which is taken from 10X's recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X's platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the GemCode sequencing workflow. Panel (a) shows a 'Molecular Barcoded Pre-amp' step where genomic DNA fragments are ligated with a barcoded left sequencing adapter and a random primer. This is followed by synthesis, denaturation, and reannealing in a thermocycle. Panel (b) shows the 'Pool' step where DNA is sheared, end-repaired, and ligated with a partial right sequencing adapter. Panel (c) shows 'Sample Indexing PCR' and 'Sample Indexing PCR to Finish Right Sequencing Adapter'. Panel (d) shows the 'Sequencing' step. Panel (e) is an 'Analysis Software Summary' showing a flow from Alignment (BWA) to Barcode Processing, Phasing (Use Existing VCFs), SV Calling, and finally BAM VCF BEDPE. A red box highlights the first two panels (a and b) with the text 'Reaction within at least one plug'.</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b>amplify the DNA</b> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as</i></b></li> </ul>

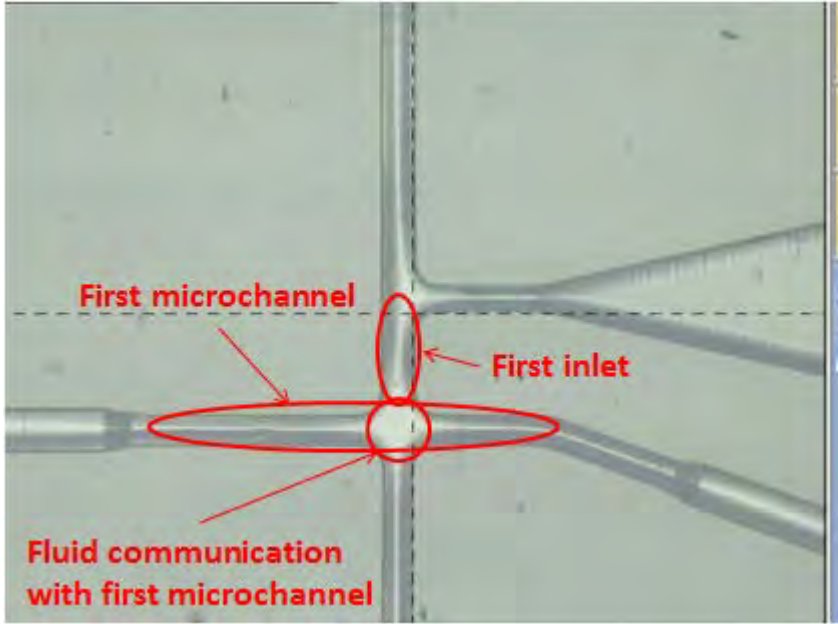
	'091 Claim Language	Infringement Support
		<p><i>the gel bead fall apart prime off of the genome and do a low-level of copying.</i> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 440 1669 1097"> <p>Low-input Molecular Barcoding in GEMs</p> <p>Reaction within at least one plug</p>  <p>10X GENOMICS</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x’s website depicts the microfluidic system wherein plugs are received in a “dynamic reaction chamber” wherein a “massive number of dynamic reactions” occur.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>Ex. 39 [10X Website Excerpts] at 1.</p>
091-36b	introducing a carrier-fluid into a first microchannel of a device;	<p>10X's GemCode platform provides "introducing a carrier-fluid into a first microchannel of a device."</p> <ul style="list-style-type: none"> <li>• The carrier fluid is the oil.</li> <li>• The first microchannel is the channel that intersects perpendicularly with the central channel and that carries the oil.</li> </ul> <p><b><u>10X's GemCode platform introduces an oil ("carrier fluid") into a first channel of a microfluidic chip.</u></b></p> <ul style="list-style-type: none"> <li>• During his August webinar, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the <i>channel in our microfluidic chip</i>." <i>Id.</i> at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And <i>on the third input well the user puts in the oil provided again by 10X</i>. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" <i>Id.</i> at 9:48-10:39. Thus, the channel containing the oil (which is a "carrier fluid immiscible with the aqueous</li> </ul>

	'091 Claim Language	Infringement Support
		<p>solutions”) intersects and flows into the channel containing the aqueous solution of the gel beads, biochemical reagents and DNA.</p> <div data-bbox="793 370 1667 1029"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div> <ul style="list-style-type: none"> <li>• In the figure above the channel containing the continuously flowing oil is shown in grey.</li> <li>• The figure below from 10x’s website further notes the continuously flowing oil from a second channel shown in light grey.</li> </ul>

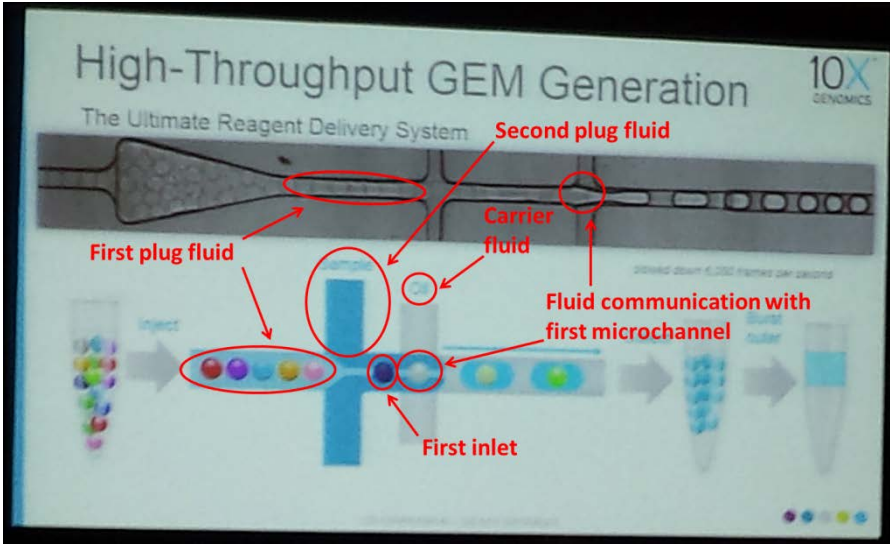
	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1818 570"> </div> <p data-bbox="787 618 1253 654">Ex. 39 [10X Website Excerpts] at 1.</p> <ul data-bbox="741 695 1862 768" style="list-style-type: none"> <li>• Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which an oil is shown flowing into a channel of the microfluidic chip in light grey:</li> </ul> <div data-bbox="787 802 1671 1344"> </div> <p data-bbox="787 1382 1268 1417">Ex. 37 [JP Morgan presentation] at 2.</p>

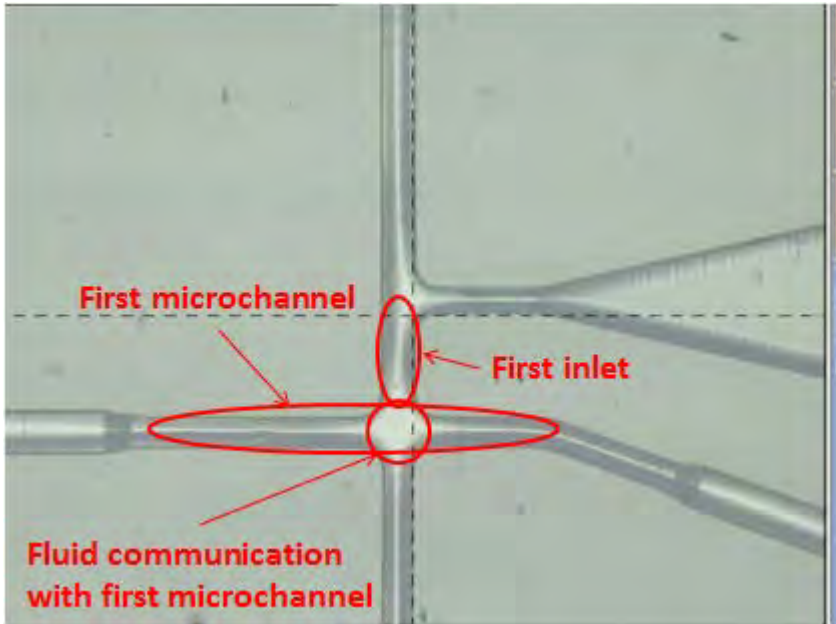


	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. The oil carrier fluid is introduced into what has been labeled "first microchannel."</li> </ul>  <p>The image is a micrograph of a microfluidic device. It shows a central vertical channel that splits into two horizontal channels. A red oval highlights the junction where the vertical channel meets the horizontal channels, with a red arrow pointing to it labeled "First inlet". Another red oval highlights one of the horizontal channels, with a red arrow pointing to it labeled "First microchannel". A third red oval highlights the junction where the horizontal channel meets the vertical channel, with a red arrow pointing to it labeled "Fluid communication with first microchannel".</p>
091-36c	simultaneously	10X's GemCode platform "simultaneously introduc[es] at least two streams of plug-fluids into

	'091 Claim Language	Infringement Support
	<p>introducing at least two streams of plug-fluids into a first inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier fluid at a junction of the first inlet and the first microchannel; wherein:</p>	<p>a first inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier-fluid after the streams contact the carrier-fluid”</p> <ul style="list-style-type: none"> <li>• There are at least three streams of aqueous fluid in 10X’s product: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads. Any two of these fluids may be chosen as the first and second plug fluid. The designations of the first, second, and third fluids in the figures in this chart are arbitrary.</li> <li>• The three plug fluids are introduced into an inlet that perpendicularly intersects (and is hence in fluid communication with) the first microchannel that carries the oil carrier fluid.</li> <li>• The plugs are the droplets (which 10X sometimes refer to as GEMs) that form at the junction between the inlet and the carrier fluid stream.</li> </ul> <p><b><u>10X’s GemCode platform simultaneously introduces three streams of plug fluid into a first inlet</u></b></p> <ul style="list-style-type: none"> <li>• During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the channels in our microfluidic chip.” Ex. 4 [10X Webinar] at 9:33-39. “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads.</i> This is a reagent delivered by 10x. <i>On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly.</i> They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.” <i>Id.</i> at 9:48-10:39. Thus, two streams of plug-fluids, the first containing biochemical reagents and DNA, and the second containing an aqueous solution of the gel beads, are introduced into the same central inlet channel.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="798 261 1675 922"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>Second plug fluid</p> <p>First plug fluid</p> <p>First inlet</p> <p>Enzyme</p> <p>GEMs</p> <p>Collect</p> <p>Cycle</p> <p>Pool</p> <p>Barcoded primer library</p> <p>DNA</p> <p>Oil</p> <p>Fluid communication with first microchannel</p> <p>Third plug fluid</p> <p>Solid phase reagent delivery</p> <p>Fluid partitioning</p> <p>Liquid phase biochemistry</p> <p>Carrier fluid</p> <p>10x GENOMICS</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x's website further notes the introduction of two streams through a central channel.</li> </ul> <div data-bbox="787 1107 1814 1414"> <p>Third plug fluid</p> <p>First plug fluid</p> <p>First inlet</p> <p>Fluid communication with first microchannel</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>Carrier fluid</p> <p>Barcoded primer library</p> <p>Barcoded GEMs</p> <p>Dissolve</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> </div>

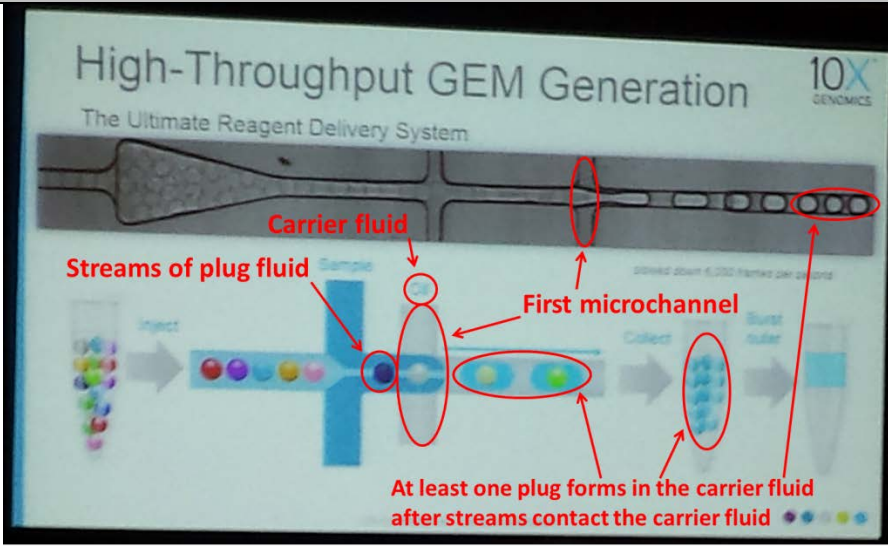
	'091 Claim Language	Infringement Support
		<p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which two streams are introduced to a middle inlet channel.</li> </ul>  <p>Ex. 37 [JP Morgan presentation] at 2.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first and second stream of plug fluid are introduced into</li> </ul>

	'091 Claim Language	Infringement Support
		<p>what is labeled “first inlet.” Those streams are in fluid communication with the “first microchannel.”</p>  <p>The image is a micrograph showing a microfluidic junction. A horizontal channel on the left is labeled "First microchannel" with a red arrow. A vertical channel from the top is labeled "First inlet" with a red arrow. At the junction, a red oval highlights the area where the two channels meet, with a label "Fluid communication with first microchannel" and a red arrow pointing to it. The junction is surrounded by other channels and structures.</p> <p><b><u>The streams of plug fluid are in fluid communication with the first channel containing the oil (“carrier-fluid”) such that droplets (“plugs”) form in the oil at the junction between the first microchannel and the inlet</u></b></p> <ul style="list-style-type: none"> <li>• The '091 patent’s description of “plugs” includes the following: “‘Plugs’ in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible.” Ex. 11 [’091 patent] at 9:20-23.</li> </ul>

	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '091 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>" <i>Id.</i> at 9:48-10:39.</li> </ul>

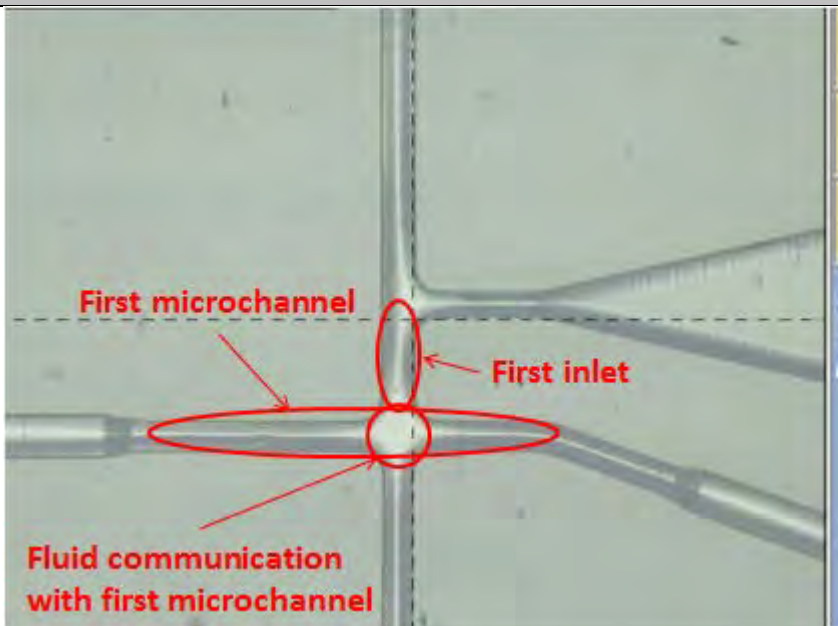
	'091 Claim Language	Infringement Support
		<div data-bbox="793 261 1661 922"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>The diagram illustrates the 10x Genomics microfluidic process. It starts with a 'Barcoded primer library' (represented by a vial of colored beads) and 'DNA' (represented by a blue line). These are combined in a 'First microchannel' where 'Streams of plug fluid' (colored beads) and 'Carrier fluid' (blue line) intersect. An 'Enzyme' is added to the mixture. The process then moves to a 'GEMs' (Gel Bead-in-emulsion) stage, where 'At least one plug forms in the carrier fluid after streams contact the carrier fluid'. This is followed by a 'Collect' stage, where the droplets are collected into a vial. The final steps are 'Cycle' and 'Pool', leading to a vial of blue liquid. The process is divided into three main stages: 'Solid phase reagent delivery', 'Fluid partitioning', and 'Liquid phase biochemistry'. The 10x Genomics logo is visible in the bottom left corner.</p> </div> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows that plugs are formed after the two inlet streams of plug fluid intersect the oil, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul>



	'091 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan presentation] at 2.</p>
091-36d	-a first plug-fluid comprises a first reagent;	<p>10X's GemCode platform has a first plug fluid that comprises a first reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the first plug fluid comprising a first reagent. The designations of the first plug fluid, second plug fluid,</li> </ul>

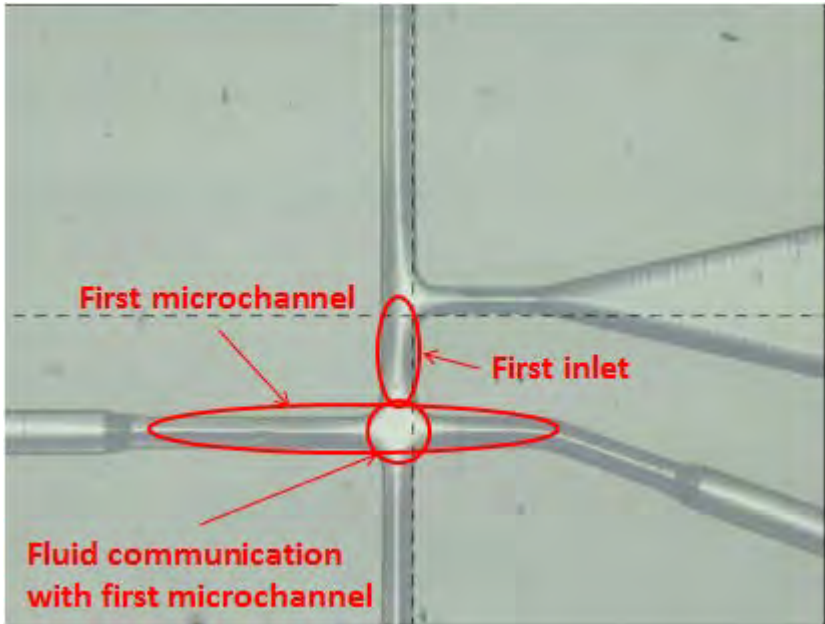
	'091 Claim Language	Infringement Support
		<p>and third plug fluid in this chart are arbitrary.</p> <p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead." <i>Id.</i> at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="798 261 1675 922" data-label="Diagram"> <p>The diagram illustrates a microfluidic system for assembling reactions. It shows a 'Barcoded primer library' being introduced into a channel. A 'First plug fluid' (containing enzymes) and a 'Second plug fluid' (containing DNA) are also introduced. These fluids mix to form 'GEMs' (Gel Bead-in-Emulsion) droplets. The process is labeled '&gt;100,000 Reactions Assembled in &lt; 5 min'. The droplets are then 'Collect'ed and 'Cycle' and 'Pool'ed. The diagram also shows a 'Solid phase reagent delivery' step leading to 'Fluid partitioning' and 'Liquid phase biochemistry'. The 10X Genomics logo is visible in the bottom left corner.</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first stream of plug fluid is introduced from the topmost channel and is comprised of one or more reagents.</li> </ul>

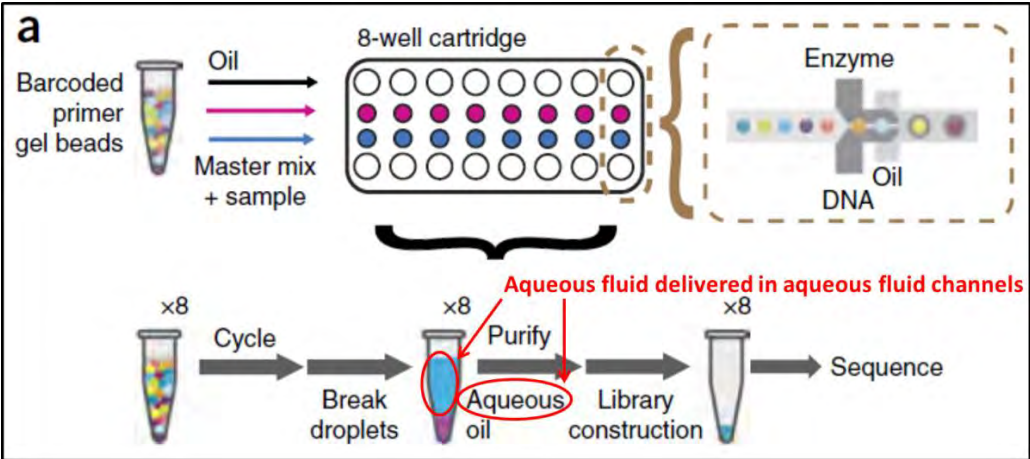
	'091 Claim Language	Infringement Support
		
091-36e	-a second plug-fluid comprises a second reagent different from the first reagent;	<p>10X's GemCode platform has a second plug fluid that comprises a second reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the second plug fluid comprising a second reagent, consistent with the choice that is made for the first plug fluid and reagent. The designations of the first plug fluid, second plug fluid, and third</li> </ul>

	'091 Claim Language	Infringement Support
		<p>plug fluid in this chart are arbitrary.</p> <p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead." <i>Id.</i> at 9:48-10:39.</li> </ul>

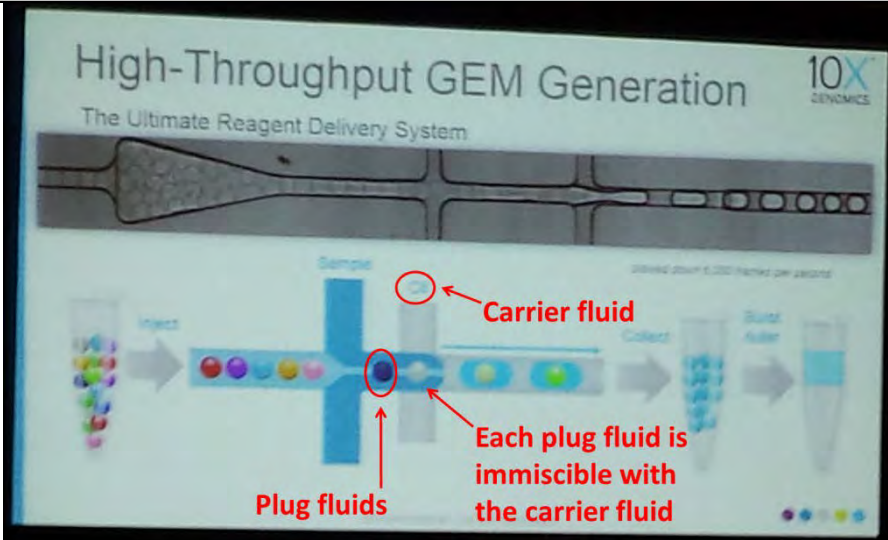
	'091 Claim Language	Infringement Support
		<div data-bbox="695 261 1675 1000"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>The diagram illustrates a microfluidic process for assembling reactions. It starts with a 'Barcoded primer library' (represented by a vial of colored beads) and a 'Third plug fluid' (containing 'Enzyme' and 'DNA', also represented by colored beads). These are combined with a 'First plug fluid' in a 'Fluid partitioning' stage. The resulting mixture is then processed through 'GEMs' (Gel Bead Emulsions) and 'Oil'. The final stage is 'Liquid phase biochemistry', which involves 'Cycling' and 'Pooling' the reactions. The 10X Genomics logo is visible in the bottom left corner of the diagram.</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A second stream of plug fluid is introduced from the top right channel and is comprised of one or more reagents that are different from the reagents in the first stream of plug fluid.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>The image is a micrograph of a microfluidic device. It shows a central vertical channel intersected by a horizontal channel. A red circle highlights the intersection point, with an arrow pointing to it from the label 'First inlet'. Another red circle highlights a section of the horizontal channel, with an arrow pointing to it from the label 'First microchannel'. A third red circle highlights the fluid within the horizontal channel, with an arrow pointing to it from the label 'Fluid communication with first microchannel'.</p>
091-36f	-each plug-fluid is immiscible with the carrier-fluid; and	<p><b><u>The three plug fluids in 10X's GemCode platform are aqueous and hence immiscible with the oil carrier fluid.</u></b></p> <ul style="list-style-type: none"> <li>In 10x's GemCode platform the channels that carry the enzyme, DNA, and barcoded gelbeads for packaging into droplets are aqueous fluid channels. This is shown in 10X's recent <i>Nature Biotechnology</i> paper, which describes the operation of 10X's GemCode platform. As explained in this paper, "[t]he first junction combines a close-packed <i>aqueous</i> slurry of gel beads with the sample and reagent mixture, and the second junction delivers the oil-surfactant solution." Ex. 5 [<i>Nature Biotechnology</i>] at 2. The droplets that are formed in 10X's microfluidic device are broken after a DNA amplification reaction is carried out inside the droplet. The fluid that is inside the droplets separates from the oil that originally surrounded and carried the droplets. As</li> </ul>

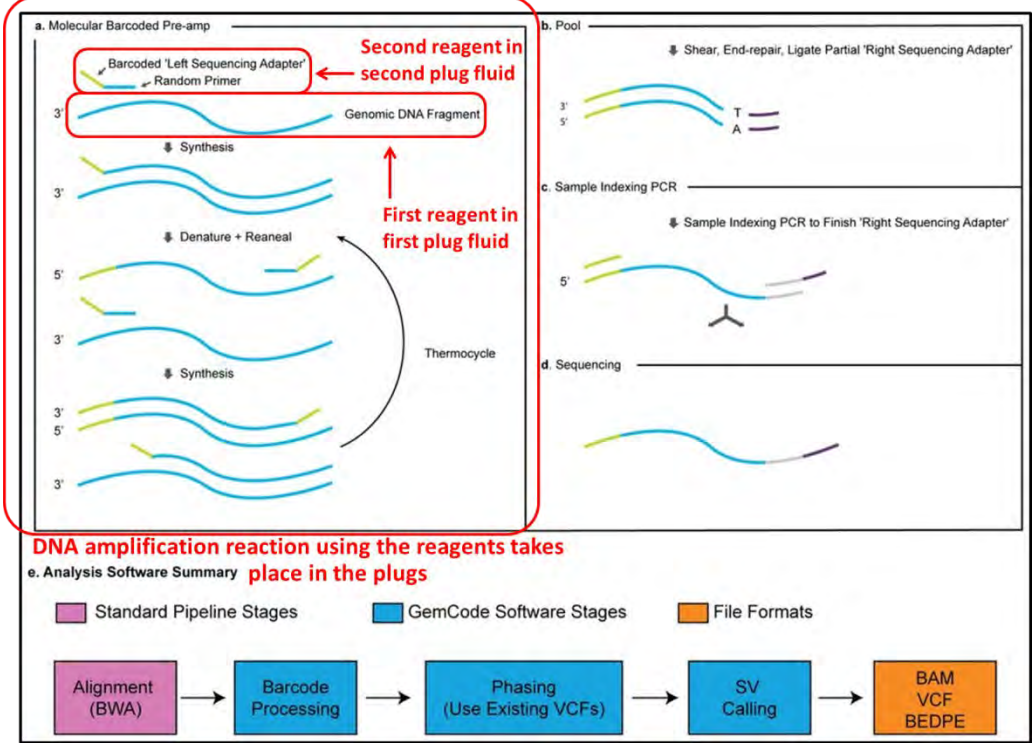


	'091 Claim Language	Infringement Support
		<p>depicted below, the interior of the droplet is “Aqueous” and is shown in blue. Thus, the channels that provided the fluids for the interior of the droplets are aqueous fluid channels.</p>  <p>Ex. 5 [<i>Nature Biotechnology</i>] at Fig. 1a.</p> <ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X’s microfluidic device forms plugs in the manner described by the ‘091 patent with reference to the below figure: “If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>” Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1669 933"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>The diagram illustrates a microfluidic process for assembling reactions. It starts with a 'Barcoded primer library' (represented by a test tube with colored beads) and 'DNA' (represented by a blue fluid). These are combined in a 'Solid phase reagent delivery' step. The process then moves to 'Fluid partitioning', where the mixture is split into droplets. The droplets are then collected and undergo 'Liquid phase biochemistry'. The final step is 'Cycle' and 'Pool', leading to a test tube with a blue liquid. The diagram also shows 'Enzyme' and 'GEMs' (Gel Bead Emulsions) being added to the mixture. A red circle highlights the intersection of the blue fluid and the oil, with a red arrow pointing to it labeled 'Oil'. Another red arrow points to the blue fluid labeled 'Carrier fluid'. A red arrow points to the colored beads labeled 'Plug fluids'. A red arrow points to the GEMs labeled 'Each plug fluid is immiscible with the carrier fluid'. The 10x Genomics logo is in the bottom left corner.</p> </div> <ul style="list-style-type: none"> <li>• As shown in the above image, the blue fluid and colored gel beads are immiscible with the oil because the intersection forms isolated droplets rather than a homogenous liquid.</li> <li>• 10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows that the plug fluids are immiscible with the oil, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are created after introducing the plug-fluid liquids to the microchannel containing the flow of oil.</li> </ul>

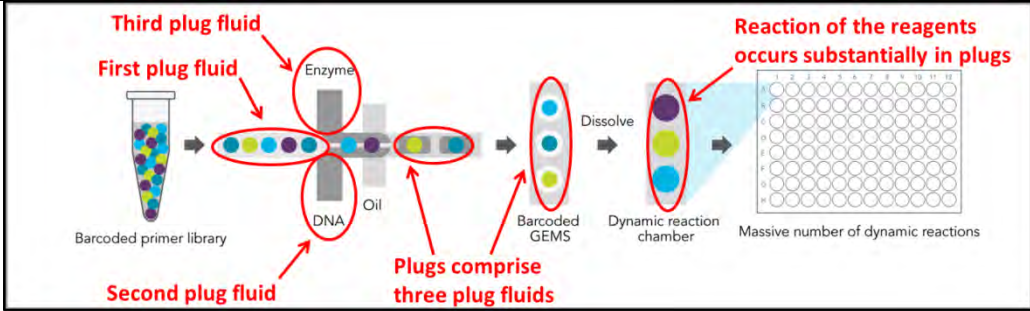
	'091 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan presentation] at 2.</p>
091-36g	<p>-each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug;</p>	<p>In 10X's GemCode platform "each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug."</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's GemCode platform: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers. All of these plug fluids are packaged into droplets, and any two of these plug fluids may be selected as the first and second plug fluid.</li> <li>• The reaction that occurs in the droplets using the reagents contained in the plug fluids is a DNA amplification reaction.</li> </ul> <p><b><u>The microfluidic droplets ("plugs") in 10X's GemCode platform comprise all three of the plug fluids that are used in 10X's product.</u></b></p> <ul style="list-style-type: none"> <li>• During his August 2015 presentation, Dr. Schnall-Levin explained that each droplet</li> </ul>

	'091 Claim Language	Infringement Support
		<p>contains a small portion of the DNA from the user and a gel bead: “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. <i>There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>” Ex. 4 [10X Webinar] at 9:48-10:39.</p> <p><b><u>10X’s GemCode platform conducts DNA amplification reactions within the microfluidic droplets (“plugs”) using the reagents from the first and second plug fluids</u></b></p> <ul style="list-style-type: none"> <li>• The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled “a. Molecular Barcoded Pre-amp,” which is taken from 10X’s recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X’s platform. The figure below shows a single stranded “Genomic DNA Fragment” that is extended through the use of a “Random Primer.” The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p><b>DNA amplification reaction using the reagents takes place in the plugs</b></p> <p><b>e. Analysis Software Summary</b></p> <p>Standard Pipeline Stages      GemCode Software Stages      File Formats</p> <pre> graph LR     A[Alignment BWA] --&gt; B[Barcode Processing]     B --&gt; C[Phasing Use Existing VCFs]     C --&gt; D[SV Calling]     D --&gt; E[BAM VCF BEDPE]   </pre> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b>amplify the DNA</b> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry</li> </ul>

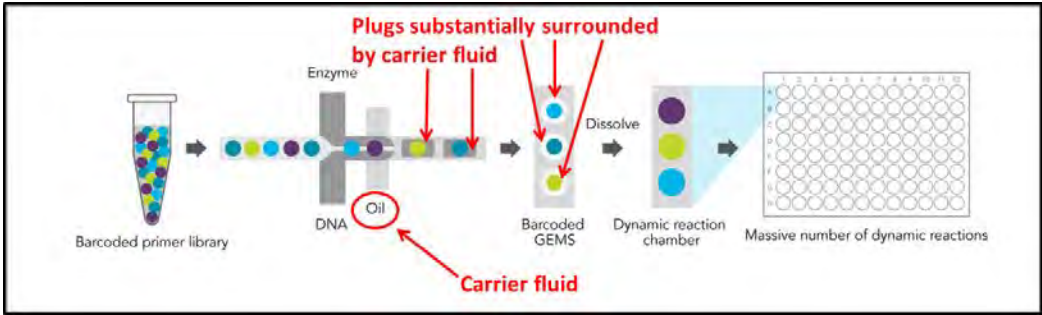
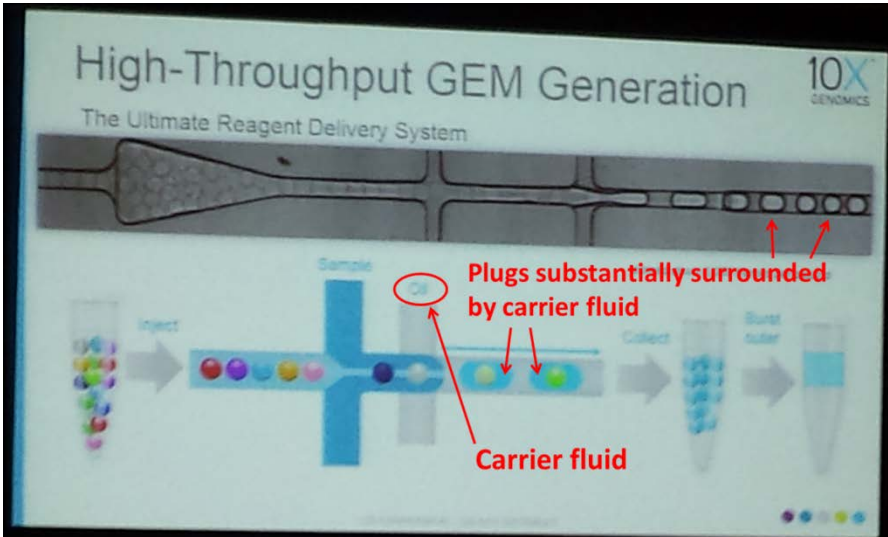
	'091 Claim Language	Infringement Support
		<p>that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 553 1671 1213" data-label="Diagram"> <p>The diagram illustrates the process of low-input molecular barcoding in GEMs (Genomic Error-Minimizing) as follows:</p> <ul style="list-style-type: none"> <li><b>Step 1: Molecular barcoding in GEMs</b> - This step is highlighted with a red box. It shows a microfluidic system where reagents from two different plug fluids (first and second) react substantially in plugs. A red arrow points to the reaction site, and a red box encloses the relevant components. A circular arrow labeled 'Cycle' indicates the process is iterative.</li> <li><b>Step 2: Pool, Ligate right adapter</b> - This step involves shearing, end-repair, A-tailing, and ligation of the right adapter. The diagram shows a DNA strand with a T overhang and an A-tail being ligated to an adapter.</li> <li><b>Step 3: Sample Indexing PCR</b> - This step involves PCR amplification of the indexed DNA. The diagram shows a DNA strand with a yellow and blue label being amplified.</li> <li><b>Step 4: Sequence and Analyze</b> - This step involves sequencing and analyzing the resulting DNA molecules. The diagram shows a DNA strand with a yellow and blue label being sequenced.</li> </ul> <p>The 10X GENOMICS logo is visible in the bottom left corner of the diagram.</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x's website depicts the microfluidic system wherein plugs are received in a "dynamic reaction chamber" wherein a "massive number of dynamic reactions" occur.</li> </ul>



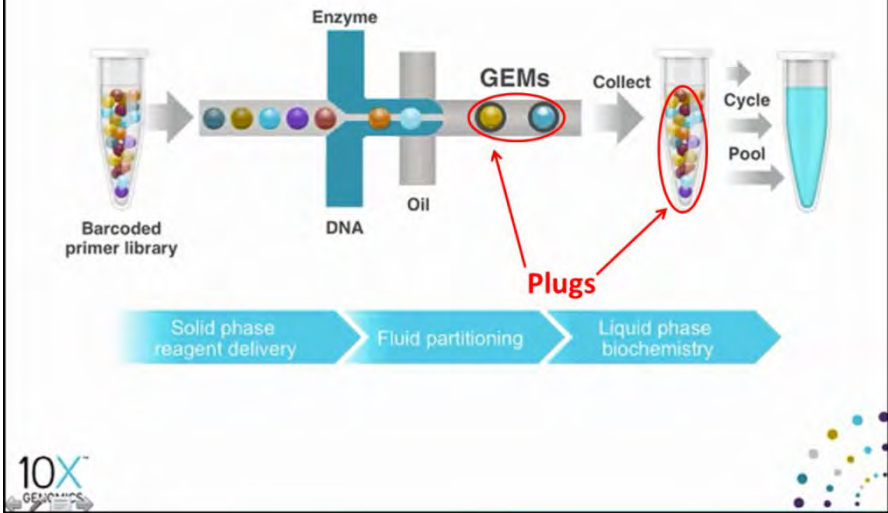
	'091 Claim Language	Infringement Support
		 <p><i>Id.</i> at 1.</p>
091-36h	-each plug is substantially surrounded by carrier.	<p><b><u>10X's GemCode platform forms microfluidic droplets ("plugs") such that the droplets are substantially surrounded by the oil.</u></b></p> <ul style="list-style-type: none"> <li>The '091 patent's description of "plugs" includes the following: "Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 11 ['091 patent] at 9:20-23.</li> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the same manner as the '091 patent. The process is depicted in the figure below. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>



	'091 Claim Language	Infringement Support
		<div data-bbox="787 297 1671 967" data-label="Diagram"> <p>The diagram illustrates the 10X Genomics GemCode system. It shows a process where a barcoded primer library, DNA, and enzymes are combined and partitioned into microfluidic droplets (GEMs) surrounded by a carrier fluid (oil). The GEMs are then collected, cycled, and pooled for sequencing. The diagram is divided into three phases: Solid phase reagent delivery, Fluid partitioning, and Liquid phase biochemistry.</p> </div> <ul style="list-style-type: none"> <li>As shown in the image above, each microfluidic droplet or plug is called a “GEM” and is substantially surrounded by the grey oil, which is the carrier fluid.</li> </ul> <p>The partitioning of DNA into droplets by 10X’s GemCode system according to the foregoing methods is also established by other resources. For instance, 10x’s website states “The 10X Genomics reagent delivery system randomly partitions DNA fragments, then prepares sequencing libraries in parallel such that all molecules produced within a partition share a unique, partition-specific barcode.” Ex. 39 [10x Website Excerpts] at 1. The website further states that the 10x chip kit “[c]ontains the microfluidic chips and accessories required for <i>sample partitioning</i>.” <i>Id.</i> at 5. 10x’s website further shows the formation of the claimed plugs:</p>

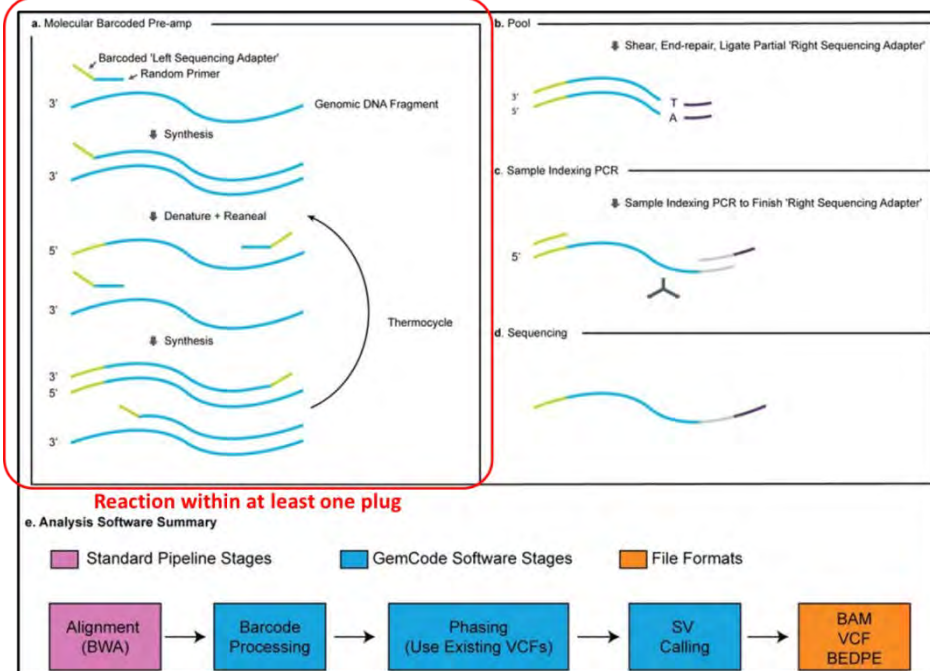
	'091 Claim Language	Infringement Support
		 <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' JP Morgan presentation further shows the plugs emerging from the junction of the oil (shown in gray) and the aqueous fluid containing the reagents (shown in blue):</li> </ul> 

	'091 Claim Language	Infringement Support
		Ex. 37 [JP Morgan presentation] at 2.
091-37a	37. A method of conducting a reaction within at least one plug comprising the steps of:	<p>10X's GemCode platform uses "method of conducting a reaction within at least one plug."</p> <ul style="list-style-type: none"> <li>• The plugs are microfluidic droplets that are formed in 10X's GemCode platform.</li> <li>• A reaction that is conducted in the plug is a DNA amplification reaction.</li> </ul> <p><b><u>10X's GemCode platform is a microfluidic system using "plugs," which 10X refers to as droplets or "GEMs".</u></b></p> <ul style="list-style-type: none"> <li>• The '091 patent's description of "plugs" includes the following: "'Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 11 ['091 patent] at 9:20-23.</li> <li>• On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '091 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>" <i>Id.</i> at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<p data-bbox="835 305 1514 345">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <ul style="list-style-type: none"> <li data-bbox="741 971 1896 1149">10x's website is consistent with Dr. Schnall-Levin's description of 10X's Platform. 10X's website states that "[t]he instrument features precise <i>microfluidics</i> coupled with single button, user-friendly operation." Ex. 39 [10X Website Excerpts] at 3. The website further states that the 10X chip kit "[c]ontains the <i>microfluidic chips</i> and accessories required for sample partitioning." <i>Id.</i> at 5.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 264 1812 573"> <p>Reaction within at least one plug</p> <p>Barcoded primer library</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>Plugs</p> <p>Barcoded GEMS</p> <p>Dissolve</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> </div> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul> <div data-bbox="787 868 1675 1408"> <p>High-Throughput GEM Generation</p> <p>The Ultimate Reagent Delivery System</p> <p>10x GENOMICS</p> <p>Sample</p> <p>Oil</p> <p>Inject</p> <p>Collect</p> <p>Burst out</p> <p>Plugs</p> <p>Barcoded GEMS</p> <p>Dissolve</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> </div>

	'091 Claim Language	Infringement Support
		<p>Ex. 37 [JP Morgan presentation] at 2.</p> <p><b><u>10X's GemCode platform conducts DNA amplification reactions within the microfluidic droplets ("plugs")</u></b></p> <ul style="list-style-type: none"> <li>• The slide above from 10X's August 2015 presentation is entitled "&gt;100,000 <i>Reactions</i> Assembled in &lt;5 min," which demonstrates that reactions are occurring within the microfluidic droplets.</li> <li>• The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp," which is taken from 10X's recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X's platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

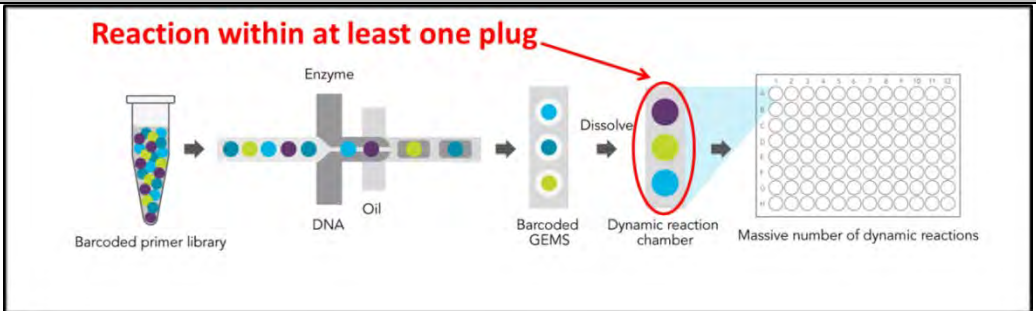
	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the 10X Genomics sequencing workflow, which is divided into five main stages:</p> <ul style="list-style-type: none"> <li><b>a. Molecular Barcoded Pre-amp:</b> This stage shows a genomic DNA fragment being amplified in droplets. A barcoded 'Left Sequencing Adapter' and a random primer are used for synthesis. The process involves denaturation and reannealing, followed by another round of synthesis. A thermocycle is indicated for this stage.</li> <li><b>b. Pool:</b> The DNA molecules are pooled, and a partial 'Right Sequencing Adapter' is ligated to the 3' end of the DNA fragment.</li> <li><b>c. Sample Indexing PCR:</b> The DNA is indexed using a sample-specific primer to finish the 'Right Sequencing Adapter'.</li> <li><b>d. Sequencing:</b> The DNA is sequenced on a high-throughput platform.</li> <li><b>e. Analysis Software Summary:</b> This stage shows the data processing pipeline. It starts with Alignment (BWA), followed by Barcode Processing, Phasing (Use Existing VCFs), SV Calling, and finally outputting BAM, VCF, and BEDPE files.</li> </ul> <p>A red box highlights the first stage (a) and the pooling stage (b), with a red arrow pointing from the text "Reaction within at least one plug" to the first stage.</p>

Ex. 5 [*Nature Biotechnology*] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to **amplify the DNA** and introduce 14-bp partition barcodes." *Id.* at 3432.

- During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling

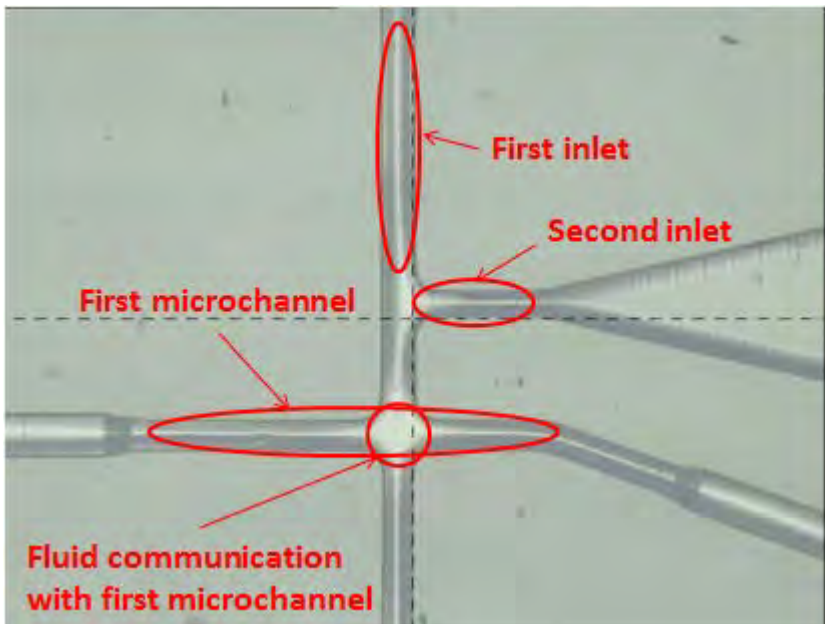


	'091 Claim Language	Infringement Support
		<p>protocol. <i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 479 1675 1140"> <p>The diagram illustrates the process of low-input molecular barcoding in GEMs. It is divided into four numbered steps:         <ol style="list-style-type: none"> <li><b>1 Molecular barcoding in GEMs:</b> Shows blue oligos binding to a light blue genomic template. A circular arrow labeled 'Cycle' is shown next to a test tube containing colorful beads.</li> <li><b>2 Pool, Ligate right adapter:</b> Shows a test tube with the template and oligos. Below it, the process is described as 'Shear, End-repair, A-tail, Ligate', with 'T' and 'A' bases indicated on the template and adapter respectively.</li> <li><b>3 Sample Indexing PCR:</b> Shows the template with the adapter ligated, and a PCR primer binding to it.</li> <li><b>4 Sequence and Analyze:</b> Shows the final sequenced template with the adapter and primer.</li> </ol>         The 10X logo is visible in the bottom left corner of the diagram.       </p> <ul style="list-style-type: none"> <li>• The figure below from 10x’s website depicts the microfluidic system wherein plugs are received in a “dynamic reaction chamber” wherein a “massive number of dynamic reactions” occur.</li> </ul> </div>

	'091 Claim Language	Infringement Support
		 <p>Ex. 39 [10X Website Excerpts] at 1.</p>
091-37b	introducing a carrier-fluid into a first microchannel of a device;	<p>10X's GemCode platform provides "introducing a carrier-fluid into a first microchannel of a device."</p> <ul style="list-style-type: none"> <li>The carrier fluid is the oil that is used in 10X's microfluidic device.</li> <li>The first microchannel is the channel through which the stream of oil is introduced perpendicularly into a stream of aqueous fluid that is packaged into droplets.</li> </ul> <p><b><u>10X's GemCode platform introduces an oil ("carrier fluid") into a first channel of a microfluidic chip.</u></b></p> <ul style="list-style-type: none"> <li>During his August webinar, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the <i>channel in our microfluidic chip</i>." <i>Id.</i> at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And <i>on the third input well the user puts in the oil provided again by 10X</i>. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" <i>Id.</i> at 9:48-10:39. Thus, the channel containing the oil (which is a "carrier fluid immiscible with the aqueous</li> </ul>

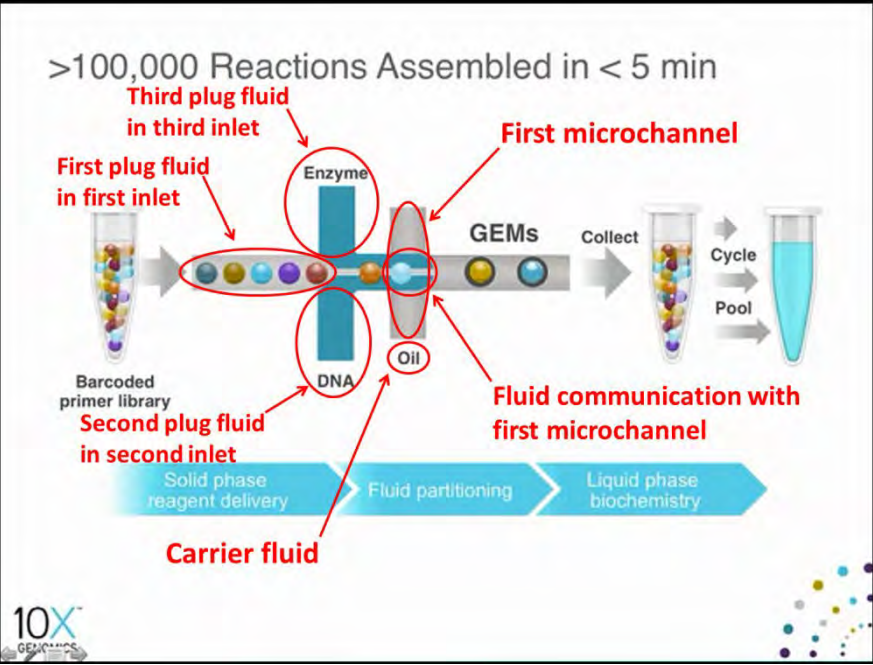
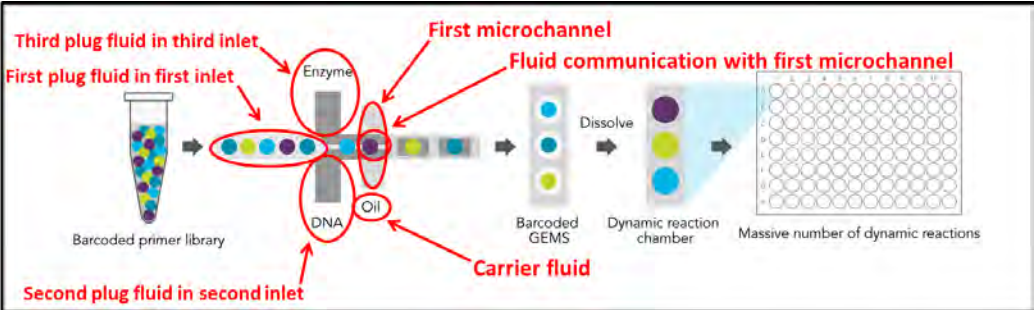
	'091 Claim Language	Infringement Support
		<p>solutions”) intersects and flows into the channel containing the aqueous solution of the gel beads, biochemical reagents and DNA.</p> <div data-bbox="793 370 1667 1032"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div> <ul style="list-style-type: none"> <li>• In the figure above the channel containing the continuously flowing oil is shown in grey.</li> <li>• The figure below from 10x’s website further notes the continuously flowing oil from a second channel shown in light grey.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1812 570"> </div> <p data-bbox="787 618 1253 651">Ex. 39 [10X Website Excerpts] at 1.</p> <ul data-bbox="743 695 1862 764" style="list-style-type: none"> <li>• Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which an oil is shown flowing into a channel of the microfluidic chip in light grey:</li> </ul> <div data-bbox="787 800 1673 1341"> </div> <p data-bbox="787 1377 1268 1411">Ex. 37 [JP Morgan presentation] at 2.</p>

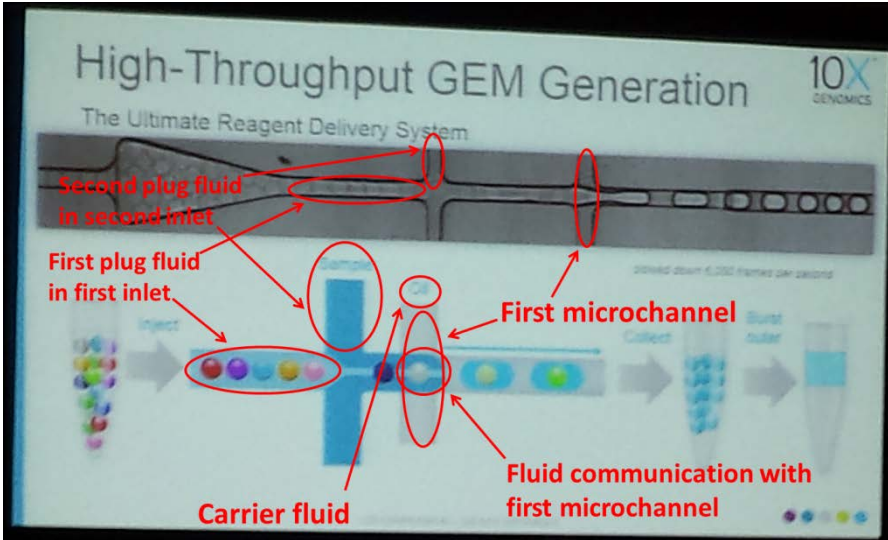
	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. The oil carrier fluid is introduced into what is labeled "first microchannel."</li> </ul>  <p>The image shows a microfluidic device with a central vertical channel. At the top, a red oval labeled "First inlet" is shown. Below it, a red oval labeled "Second inlet" is shown. A horizontal dashed line intersects the central channel. Below this line, a red oval labeled "First microchannel" is shown. At the bottom, a red oval labeled "Fluid communication with first microchannel" is shown. The device is made of clear plastic and has a ruler visible in the background.</p>
091-37c	introducing a stream of a first plug-fluid into a first	10X's GemCode platform introduces "a stream of a first plug-fluid into a first inlet in fluid communication with the first microchannel and simultaneously introducing a stream of a

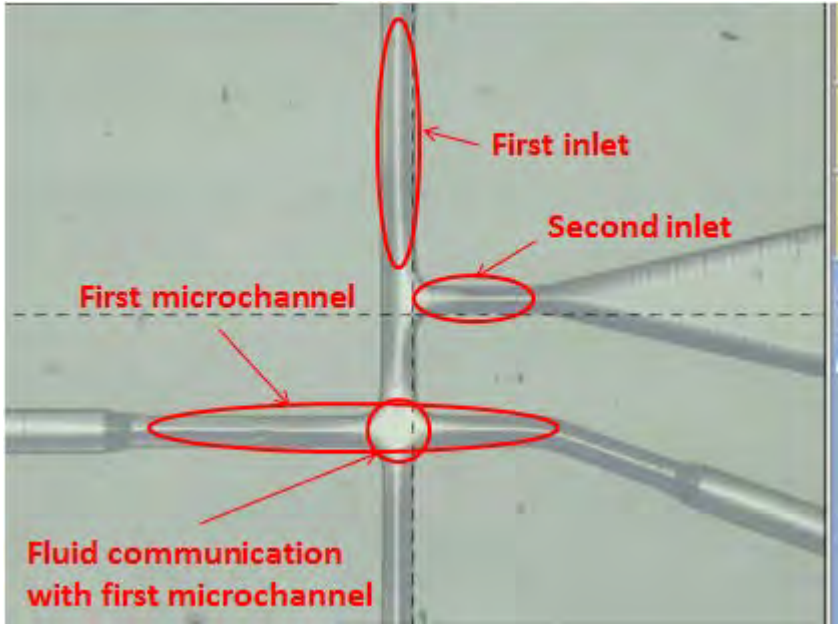
	'091 Claim Language	Infringement Support
	<p>inlet in fluid communication with the first microchannel and simultaneously introducing a stream of a second plug-fluid into a second inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier-fluid after the first and second plug-fluids contact the carrier fluid; wherein:</p>	<p>second plug-fluid into a second inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier-fluid after the first and second plug-fluids contact The carrier fluid”</p> <ul style="list-style-type: none"> <li>• There are at least three streams of aqueous fluid in 10X’s product: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads. Any two of these fluids may be chosen as the first and second plug fluid. The designations of the first, second, and third fluids in the figures in this chart are arbitrary.</li> <li>• Each of these three plug fluids are introduced via their own inlet. They combine at another inlet that perpendicularly intersects (and is hence in fluid communication with) the first microchannel that carries the oil carrier fluid.</li> <li>• The plugs are the droplets (which 10X sometimes refer to as GEMs) that form at the junction between the inlet and the carrier fluid stream.</li> </ul> <p><b><u>10X’s GemCode platform simultaneously introduces at least two streams of plug fluid via at least two inlets</u></b></p> <ul style="list-style-type: none"> <li>• During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the channels in our microfluidic chip.” Ex. 4 [10X Webinar] at 9:33-39. “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads.</i> This is a reagent delivered by 10x. <i>On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly.</i> They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.” <i>Id.</i> at 9:48-10:39. Thus, two streams of plug-fluids, the first containing biochemical reagents and DNA, and the second containing an aqueous solution of the gel beads, are introduced into the same central inlet channel.</li> </ul>



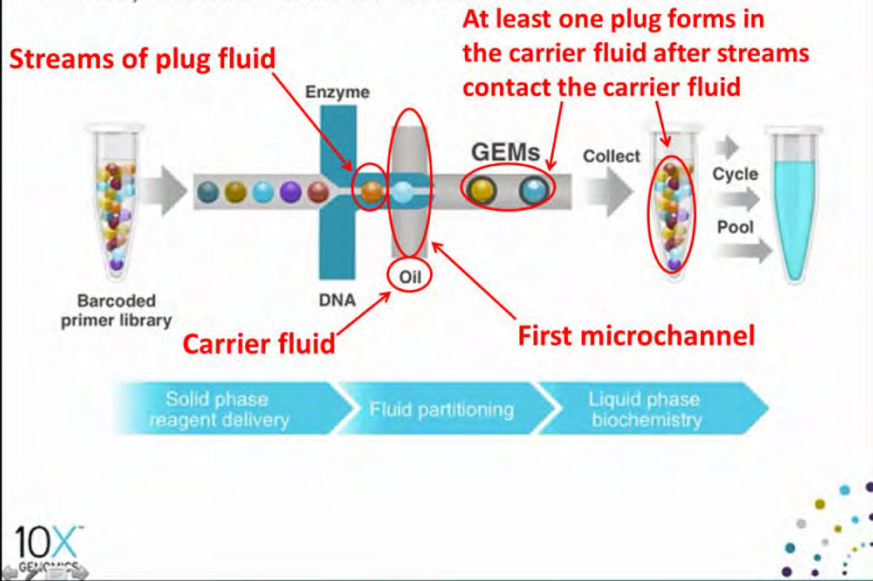
	'091 Claim Language	Infringement Support
		<p data-bbox="846 305 1514 342">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <ul data-bbox="743 964 1839 1032" style="list-style-type: none"> <li>The figure below from 10x's website further notes the introduction of two streams through a central channel.</li> </ul> 

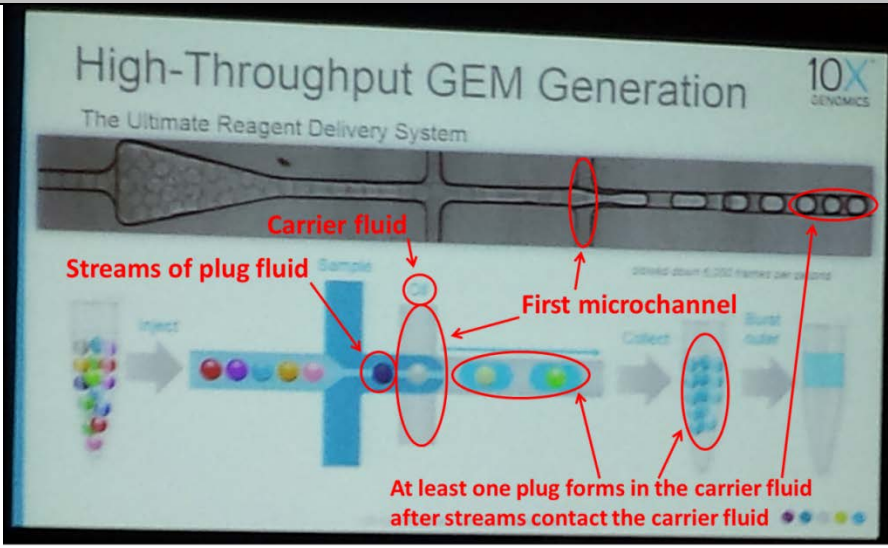


	'091 Claim Language	Infringement Support
		<p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which two streams are introduced to a middle inlet channel.</li> </ul>  <p>Ex. 37 [JP Morgan presentation] at 2.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first stream of plug fluid is introduced into</li> </ul>

	'091 Claim Language	Infringement Support
		<p>what is labeled as the “first inlet” and a second stream of plug fluid is introduced into the “second inlet.” The first and second streams of plug fluid are in “fluid communication with the first microchannel.”</p>  <p><b><u>The three inlets are in fluid communication with the first channel containing the oil (“carrier-fluid”) such that droplets (“plugs”) form in the oil after the first and second streams of plug fluid contact the oil</u></b></p> <ul style="list-style-type: none"> <li>The '091 patent’s description of “plugs” includes the following: “‘Plugs’ in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible.” Ex. 11 [’091 patent] at 9:20-23.</li> </ul>

	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '193 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>" <i>Id.</i> at 9:48-10:39.</li> </ul>

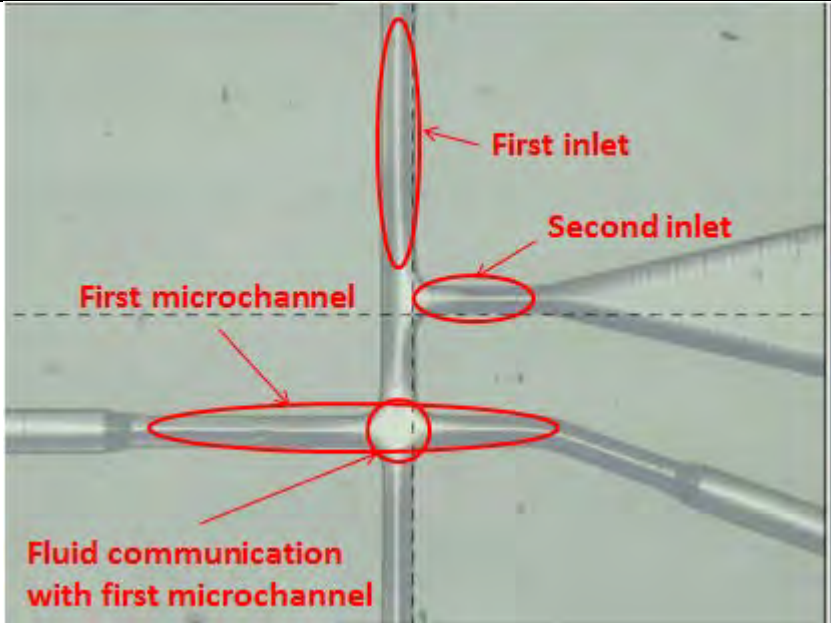
	'091 Claim Language	Infringement Support
		<p data-bbox="848 305 1514 342">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p>The diagram illustrates the 10x Genomics microfluidic process. It shows a 'Barcoded primer library' being introduced into a 'First microchannel' along with 'Enzyme' and 'DNA'. 'Streams of plug fluid' are shown intersecting a 'Carrier fluid' which contains 'Oil'. This results in 'GEMs' (Gel Bead-in-emulsion) where 'At least one plug forms in the carrier fluid after streams contact the carrier fluid'. The process then moves to 'Collect', 'Cycle', and 'Pool' stages. A timeline at the bottom shows 'Solid phase reagent delivery', 'Fluid partitioning', and 'Liquid phase biochemistry'. The 10x Genomics logo is in the bottom left corner.</p> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows that plugs are formed after the two inlet streams of plug fluid intersect the oil, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan presentation] at 2.</p>
091-37d	-a first plug-fluid comprises a first reagent;	<p>10X's GemCode platform has a first plug fluid that comprises a first reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the first plug fluid comprising a first reagent. The designations of the first plug fluid, second plug fluid, and third plug fluid in this chart are arbitrary.</li> </ul>

	'091 Claim Language	Infringement Support
		<p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead." <i>Id.</i> at 9:48-10:39.</li> </ul>

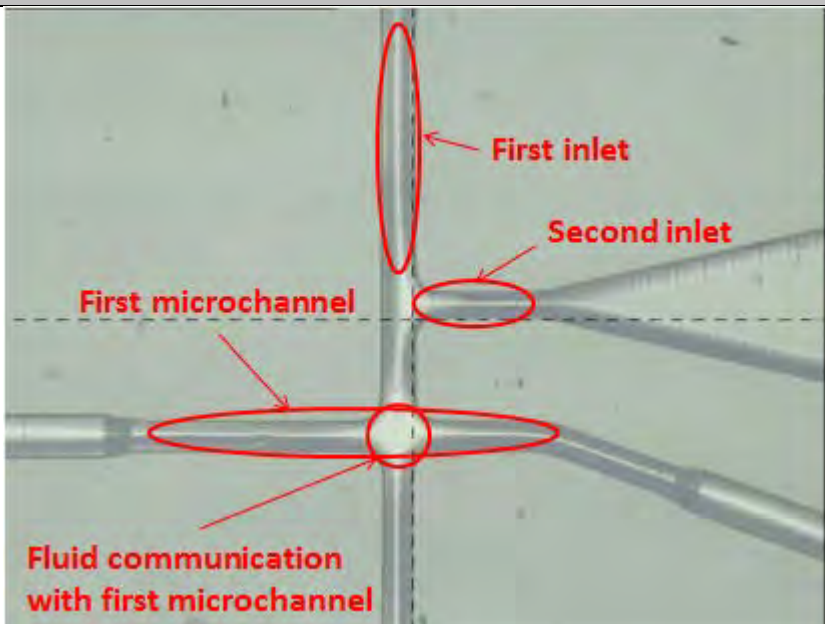
	'091 Claim Language	Infringement Support
		<div data-bbox="793 261 1675 927"> <p>The diagram illustrates a microfluidic system for assembling reactions. It shows three inlets at the top: 'First plug fluid in first inlet', 'Second plug fluid in second inlet', and 'Third plug fluid in third inlet'. A 'Carrier fluid' inlet is at the bottom. The system consists of a central cross-shaped junction. The top arm contains an 'Enzyme' reservoir. The left arm contains a 'DNA' reservoir. The right arm contains an 'Oil' reservoir. The bottom arm contains a 'GEMs' reservoir. The flow is indicated by arrows: 'First plug fluid in first inlet' flows into the top arm, 'Second plug fluid in second inlet' flows into the left arm, and 'Third plug fluid in third inlet' flows into the right arm. The 'Carrier fluid' flows into the bottom arm. The flow from the top arm and left arm is labeled 'Solid phase reagent delivery'. The flow from the right arm is labeled 'Fluid partitioning'. The flow from the bottom arm is labeled 'Liquid phase biochemistry'. The final product is a 'GEMs' reservoir, which is then 'Collect'ed into a tube, 'Cycle'd, and 'Pool'ed into a larger tube. The diagram also shows a 'Barcoded primer library' reservoir on the left. The 10X Genomics logo is in the bottom left corner.</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first stream of plug fluid is introduced into what is labeled as the "first inlet" and is comprised of one or more reagents.</li> </ul>

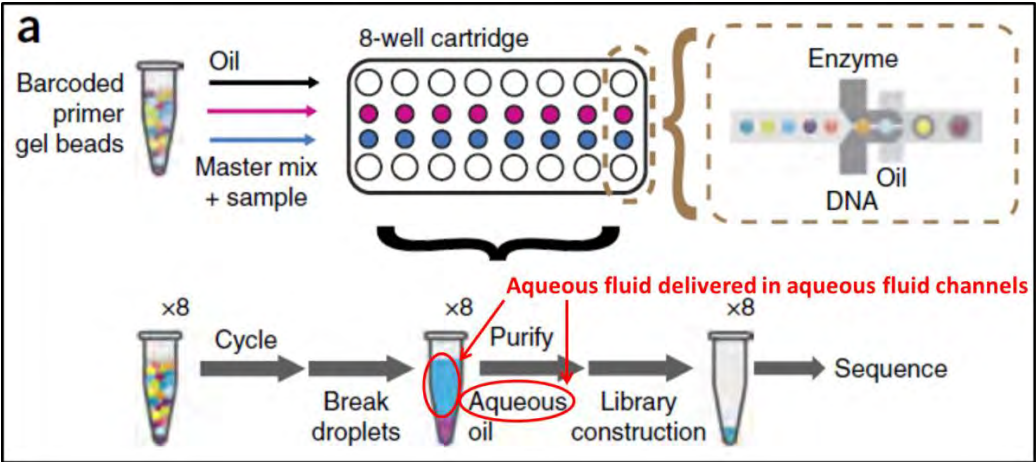


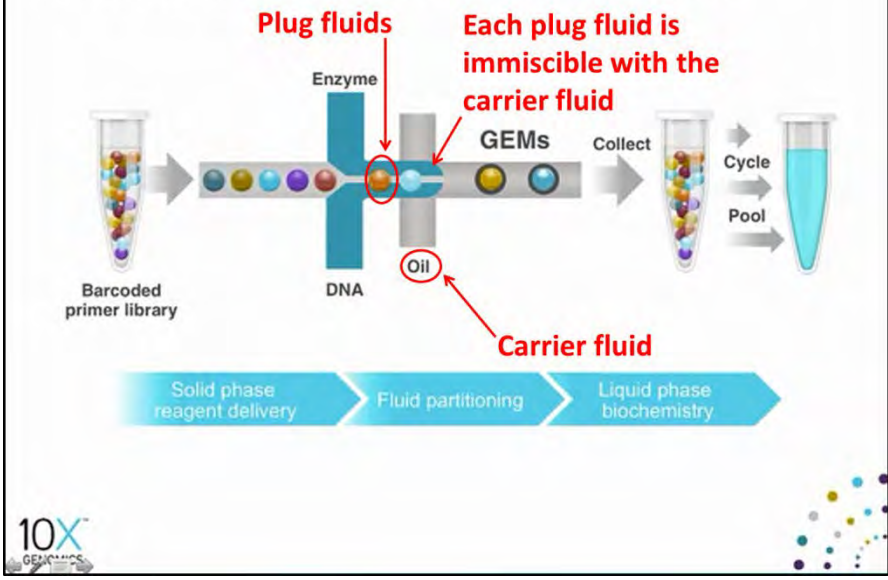
	'091 Claim Language	Infringement Support
		
091-37e	-a second plug-fluid comprises a second reagent;	<p>10X's GemCode platform has a second plug fluid that comprises a second reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the second plug fluid comprising a second reagent, consistent with the choice that is made for the first plug fluid and reagent. The designations of the first plug fluid, second plug fluid, and third</li> </ul>

	'091 Claim Language	Infringement Support
		<p>plug fluid in this chart are arbitrary.</p> <p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead." <i>Id.</i> at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1675 933"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>First plug fluid in first inlet</p> <p>Third plug fluid in third inlet</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>GEMs</p> <p>Collect</p> <p>Cycle</p> <p>Pool</p> <p>Barcoded primer library</p> <p>Solid phase reagent delivery</p> <p>Fluid partitioning</p> <p>Liquid phase biochemistry</p> <p>10X GENOMICS</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A second stream of plug fluid is introduced into what is labeled as the "second inlet" and is comprised of one or more reagents.</li> </ul>

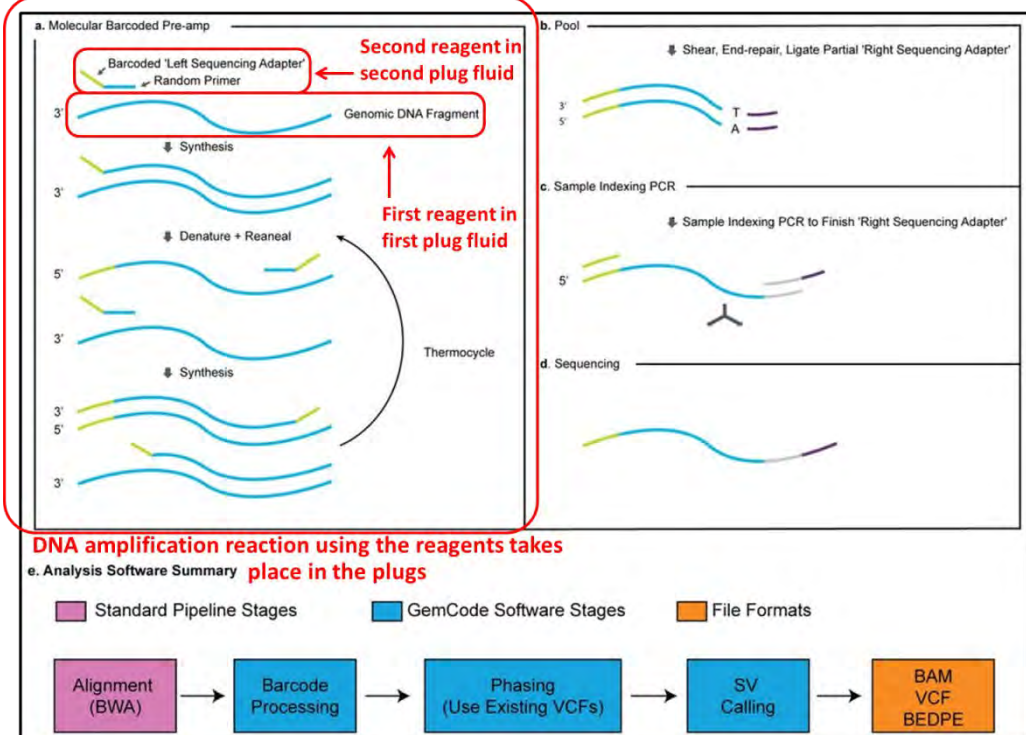
	'091 Claim Language	Infringement Support
		 <p>The micrograph shows a microfluidic device with several channels. A horizontal channel on the left is labeled 'First microchannel'. A vertical channel at the top is labeled 'First inlet'. A smaller horizontal channel on the right is labeled 'Second inlet'. A red oval highlights a junction where the first microchannel and the first inlet meet, with an arrow pointing to it labeled 'Fluid communication with first microchannel'.</p>
091-37f	-each plug-fluid is immiscible with the carrier-fluid;	<p><b><u>The three plug fluids in 10X's GemCode platform are aqueous and hence immiscible with the oil carrier fluid.</u></b></p> <ul style="list-style-type: none"> <li>In 10x's GemCode platform the channels that carry the enzyme, DNA, and barcoded gelbeads for packaging into droplets are aqueous fluid channels. This is shown in 10X's recent <i>Nature Biotechnology</i> paper, which describes the operation of 10X's GemCode platform. As explained in this paper, "[t]he first junction combines a close-packed <i>aqueous</i> slurry of gel beads with the sample and reagent mixture, and the second junction delivers the oil-surfactant solution." Ex. 5 [<i>Nature Biotechnology</i>] at 2. The droplets that are formed in 10X's microfluidic device are broken after a DNA amplification reaction is carried out inside the droplet. The fluid that is inside the droplets separates from the oil that originally surrounded and carried the droplets. As</li> </ul>

	'091 Claim Language	Infringement Support
		<p>depicted below, the interior of the droplet is “Aqueous” and is shown in blue. Thus, the channels that provided the fluids for the interior of the droplets are aqueous fluid channels.</p>  <p>Ex. 5 [<i>Nature Biotechnology</i>] at Fig. 1a.</p> <ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X’s microfluidic device forms plugs in the manner described by the ‘091 patent with reference to the below figure: “If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>” Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>

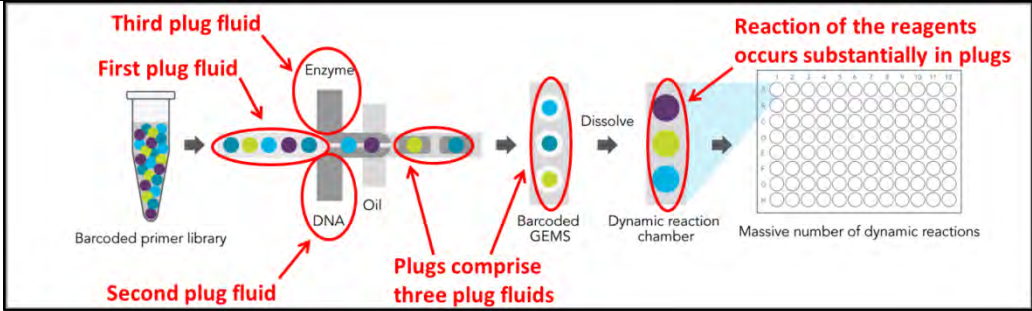
	'091 Claim Language	Infringement Support
		<p data-bbox="835 305 1514 342">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p data-bbox="787 868 871 933">10X GENOMICS</p>
091-37g	<p data-bbox="331 974 669 1185">-each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug; and</p>	<p data-bbox="690 974 1913 1039">In 10X's GemCode platform "each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug."</p> <ul data-bbox="741 1047 1902 1299" style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's GemCode platform: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers. All of these plug fluids are packaged into droplets, and any two of these plug fluids may be selected as the first and second plug fluid.</li> <li>• The reaction that occurs in the droplets using the reagents contained in the plug fluids is a DNA amplification reaction.</li> </ul> <p data-bbox="690 1339 1902 1404"><b><u>The microfluidic droplets ("plugs") in 10X's GemCode platform comprise all three of the plug fluids that are used in 10X's product.</u></b></p>

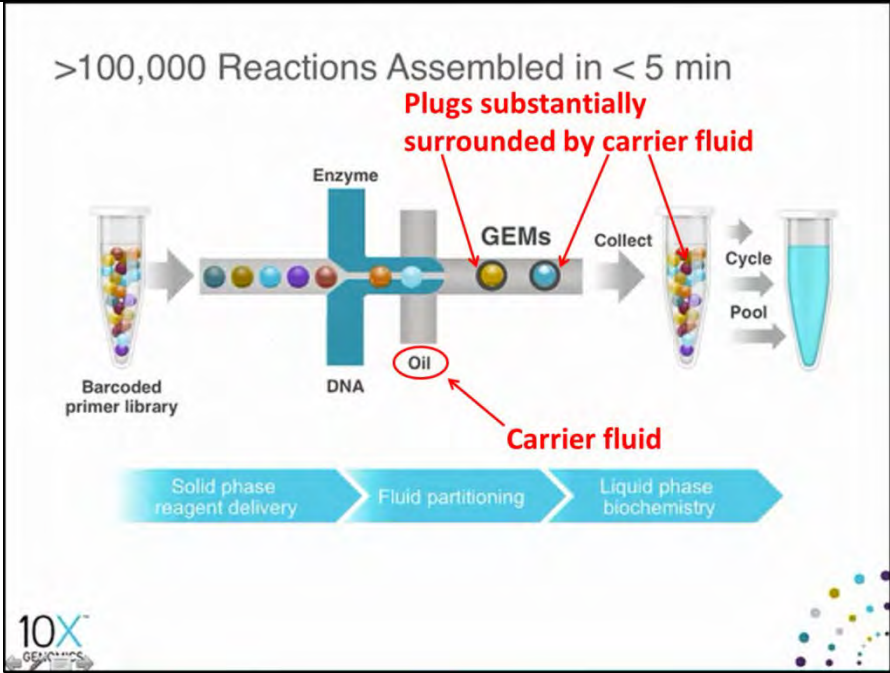
	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin explained that each droplet contains a small portion of the DNA from the user and a gel bead: “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. <i>There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>” Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul> <p><b><u>10X’s GemCode platform conducts DNA amplification reactions within the microfluidic droplets (“plugs”) using the reagents from the first and second plug fluids</u></b></p> <ul style="list-style-type: none"> <li>The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled “a. Molecular Barcoded Pre-amp,” which is taken from 10X’s recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X’s platform. The figure below shows a single stranded “Genomic DNA Fragment” that is extended through the use of a “Random Primer.” The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

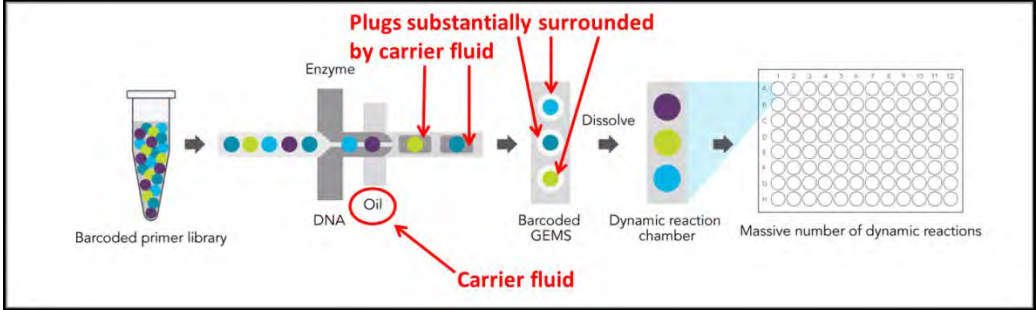
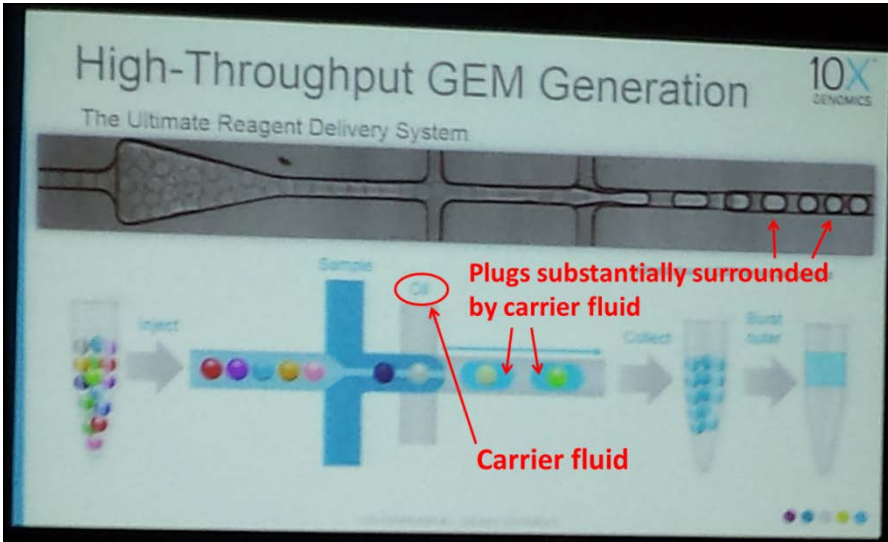


	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the GEM sequencing process in five stages:</p> <ul style="list-style-type: none"> <li><b>a. Molecular Barcoded Pre-amp:</b> A genomic DNA fragment is ligated with a barcoded left sequencing adapter and a random primer. This is followed by synthesis, denaturation, and reannealing, and then another round of synthesis. A thermocycle is indicated. Red annotations highlight the 'Second reagent in second plug fluid' (the barcoded adapter) and the 'First reagent in first plug fluid' (the random primer).</li> <li><b>b. Pool:</b> The DNA fragments are sheared, end-repaired, and ligated with a partial right sequencing adapter.</li> <li><b>c. Sample Indexing PCR:</b> The DNA is amplified with sample indexing PCR to finish the right sequencing adapter.</li> <li><b>d. Sequencing:</b> The DNA is sequenced.</li> <li><b>e. Analysis Software Summary:</b> A flowchart showing the analysis pipeline: Alignment (BWA) → Barcode Processing → Phasing (Use Existing VCFs) → SV Calling → BAM VCF BEDPE. The legend indicates: Standard Pipeline Stages (pink), GemCode Software Stages (blue), and File Formats (orange).</li> </ul> <p>Below the diagram, red text states: "DNA amplification reaction using the reagents takes place in the plugs".</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <i>amplify the DNA</i> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry</li> </ul>

	'091 Claim Language	Infringement Support
		<p>that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 548 1669 1209"> <p><b>Low-input Molecular Barcoding in GEMs</b></p> <p><b>Reaction of reagents occurs substantially in plugs</b></p> <p>1 Molecular barcoding in GEMs</p> <p>Second reagent in second plug fluid</p> <p>First reagent from first plug fluid</p> <p>2 Pool, Ligate right adapter</p> <p>Shear, End-repair, A-tail, Ligate</p> <p>3 Sample Indexing PCR</p> <p>4 Sequence and Analyze</p> <p>10X GENOMICS</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x's website depicts the microfluidic system wherein plugs are received in a "dynamic reaction chamber" wherein a "massive number of dynamic reactions" occur.</li> </ul>

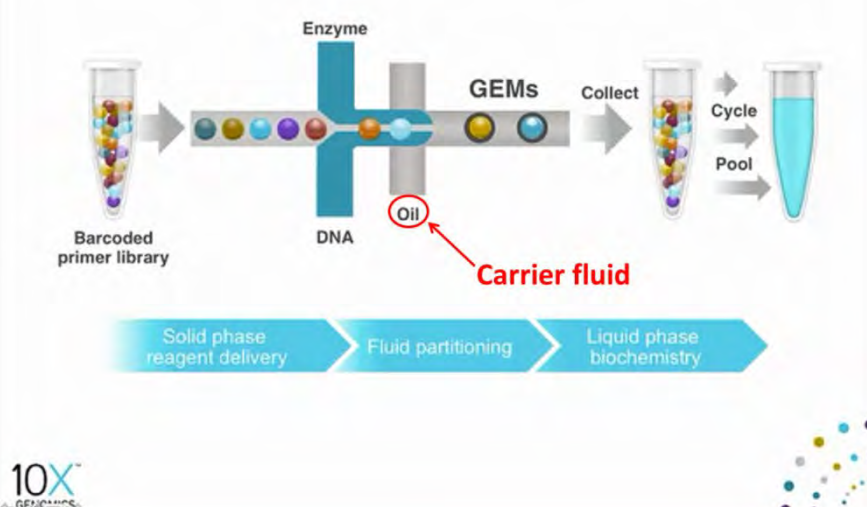
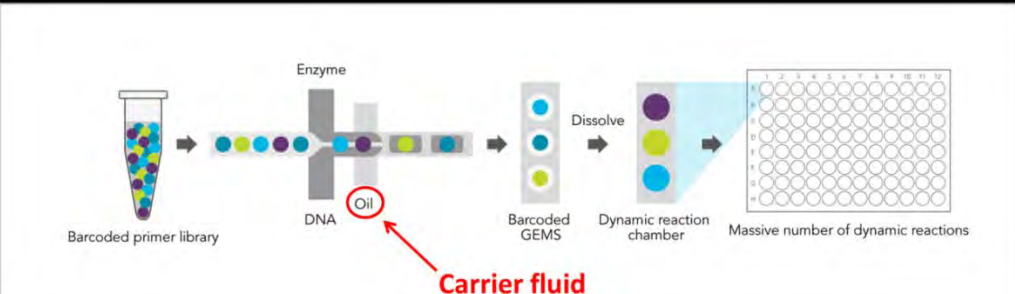
	'091 Claim Language	Infringement Support
		 <p>Ex. 39 [10X Website Excerpts] at 1.</p>
091-37h	-each plug is substantially surrounded by carrier.	<p><b><u>10X's GemCode platform forms microfluidic droplets ("plugs") such that the droplets are substantially surrounded by the oil.</u></b></p> <ul style="list-style-type: none"> <li>The '091 patent's description of "plugs" includes the following: "Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 11 ['091 patent] at 9:20-23.</li> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the same manner as the '091 patent. The process is depicted in the figure below. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1671 930"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>Plugs substantially surrounded by carrier fluid</p>  <p>Barcoded primer library</p> <p>Enzyme</p> <p>DNA</p> <p>GEMs</p> <p>Oil</p> <p>Carrier fluid</p> <p>Collect</p> <p>Cycle</p> <p>Pool</p> <p>Solid phase reagent delivery</p> <p>Fluid partitioning</p> <p>Liquid phase biochemistry</p> <p>10X GENOMICS</p> </div> <ul style="list-style-type: none"> <li>As shown in the image above, each microfluidic droplet or plug is called a “GEM” and is substantially surrounded by the grey oil, which is the carrier fluid.</li> <li>The partitioning of DNA into droplets by 10X’s GemCode system according to the foregoing methods is also established by other resources. For instance, 10x’s website states “The 10X Genomics reagent delivery system randomly partitions DNA fragments, then prepares sequencing libraries in parallel such that all molecules produced within a partition share a unique, partition-specific barcode.” Ex. 39 [10x Website Excerpts] at 1. The website further states that the 10x chip kit “[c]ontains the microfluidic chips and accessories required for <i>sample partitioning</i>.” 10x’s website further shows the formation of the claimed plugs:</li> </ul>

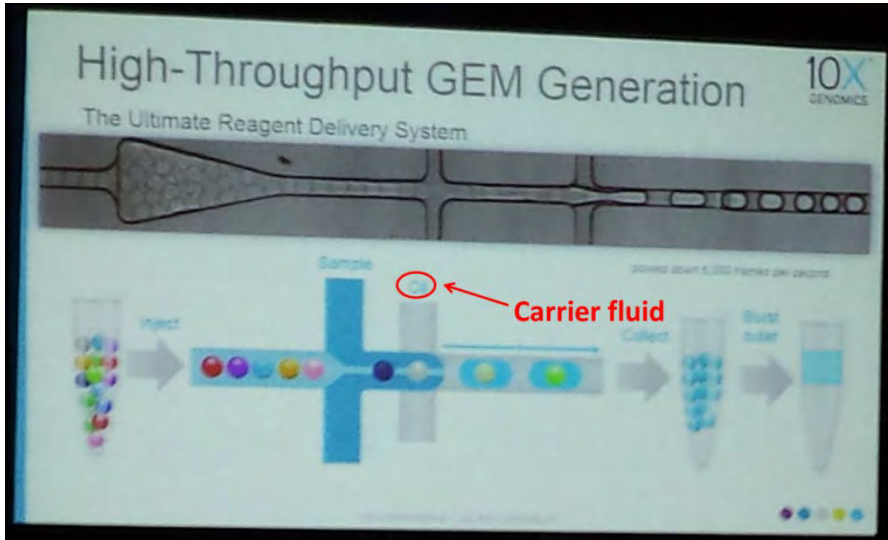
	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the process of generating Gel Emulsion Microdroplets (GEMs). It starts with a 'Barcoded primer library' (represented by a test tube with colored beads) and 'DNA' (represented by a small tube). These are combined with an 'Enzyme' and an 'Oil' phase (indicated by a red circle). The mixture is then combined with a 'Carrier fluid' (indicated by a red circle). The process results in 'Plugs substantially surrounded by carrier fluid' (indicated by red arrows). These plugs are then 'Dissolved' in a 'Dynamic reaction chamber' to produce a 'Massive number of dynamic reactions' (represented by a grid of small circles).</p> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' JP Morgan presentation further shows the plugs emerging from the junction of the oil (shown in gray) and the aqueous fluid containing the reagents (shown in blue):</li> </ul>  <p>The screenshot shows a presentation slide titled 'High-Throughput GEM Generation' by 10x Genomics. The slide features a diagram of the 'Ultimate Reagent Delivery System'. It shows a 'Sample' being injected into a 'Carrier fluid' (indicated by a red circle). The process results in 'Plugs substantially surrounded by carrier fluid' (indicated by red arrows). The plugs are then 'Collected' and 'Burst out' into a microfluidic chip (represented by a grid of small circles).</p>

	'091 Claim Language	Infringement Support
		Ex. 37 [JP Morgan presentation] at 2.
091-38	38. The method of claim 37, wherein the carrier-fluid comprises an oil.	<p><b><u>The carrier fluid in 10X's GemCode platform is an oil.</u></b></p> <ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms droplets using oil as carrier fluid. The process is depicted in the figure below. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. <i><b>And on the third input well the user puts in the oil provided again by 10X.</b></i> There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i><b>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</b></i>" Ex. 4 [10X Webinar] at 9:48-10:39. Below, two resulting droplets are shown as a yellow and a blue circle. These droplets are encased by the oil, which carries them down the channel for collection.</li> </ul>

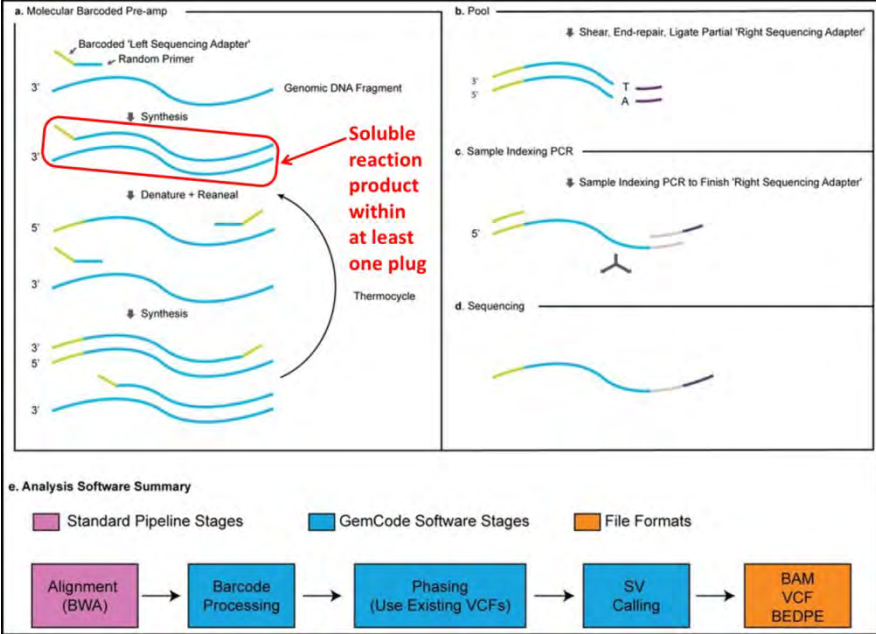


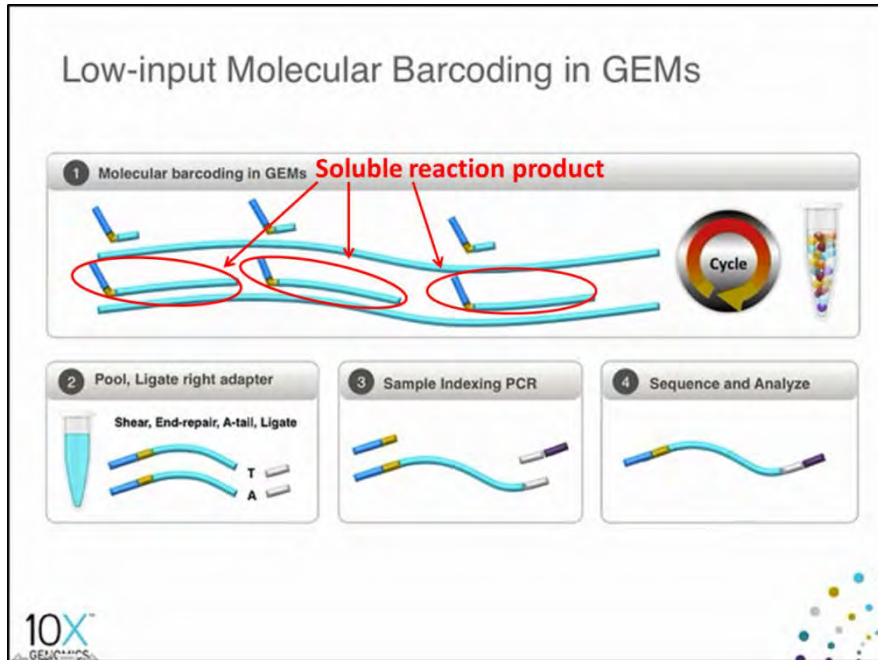
	'091 Claim Language	Infringement Support
		<p data-bbox="840 300 1512 349">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p data-bbox="735 958 1743 998">• 10X's website further portrays the "oil" carrier fluid (shown in light gray):</p> 

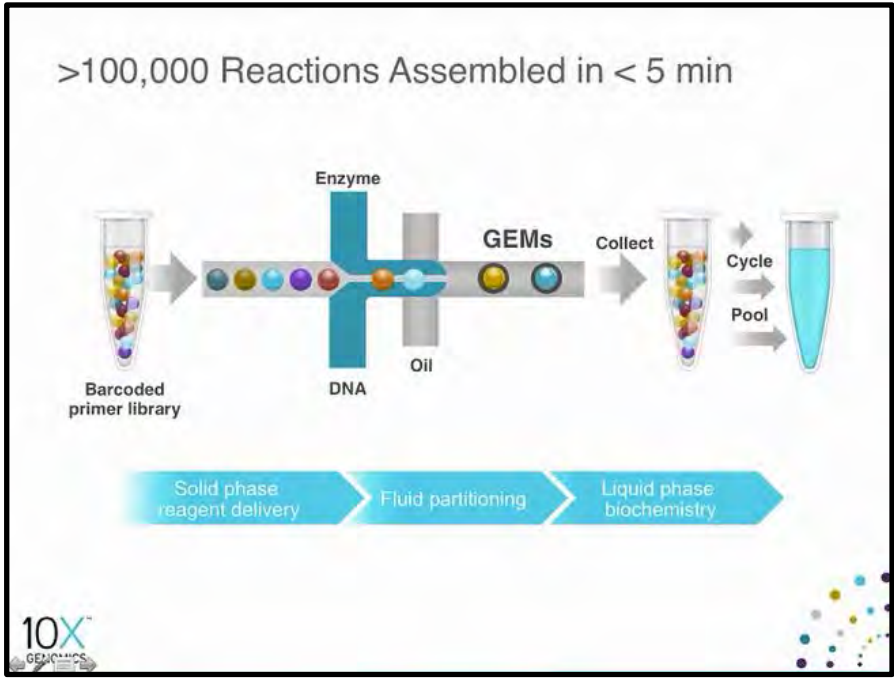


	'091 Claim Language	Infringement Support
		<p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>10X's 2015 JP Morgan presentation further shows the oil carrier fluid (shown in gray):</li> </ul> 
091-39	39. The method of claim 37, wherein the carrier-fluid comprises at least one surfactant.	<p><b><u>The 10X Genomics platform uses oil carrier fluid that comprises a surfactant.</u></b></p> <ul style="list-style-type: none"> <li>As 10X describes their system in its recent publication in <i>Nature Biotechnology</i>, an “oil-surfactant” solution is used to partition the DNA sample into droplets: “Reagent delivery and sample partitioning are performed in a plastic microfluidic consumable cartridge that processes eight samples simultaneously. Cartridge reservoirs are loaded with gel beads, the sample and reagent mixture and an <i>oil-surfactant solution</i>. Reagents are delivered from the reservoirs via a network of microfluidic channels to a microfluidic ‘double-cross’ junction (Fig. 1a). <i>The first junction combines a close-packed aqueous slurry of gel beads with the sample and reagent mixture, and the</i></li> </ul>

	'091 Claim Language	Infringement Support
		<i>second junction delivers the oil-surfactant solution.”</i> Ex. 5 [Nature Biotechnology] at 2.
091-43	43. The method of claim 37, wherein the reaction of the plug-fluids forms a soluble reaction product within at least one plug.	<p><b><u>10X’s GemCode platform forms a DNA amplification product that is soluble within the aqueous plug fluid.</u></b></p> <ul style="list-style-type: none"> <li>The DNA amplification process which occurs in the microfluidic droplets of 10X’s GemCode platform is depicted in the figure below in the panel labeled “a. Molecular Barcoded Pre-amp.” This figure is taken from 10X’s recent article in <i>Nature Biotechnology</i>, which presents data based on the use of 10X’s GemCode platform. The figure below shows a single stranded “Genomic DNA Fragment” that is extended through the use of a “Random Primer.” The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b>amplify the DNA</b> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432. The DNA that is formed via the amplification reaction is soluble in water.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schnall-Levin described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal</i></b></li> </ul>

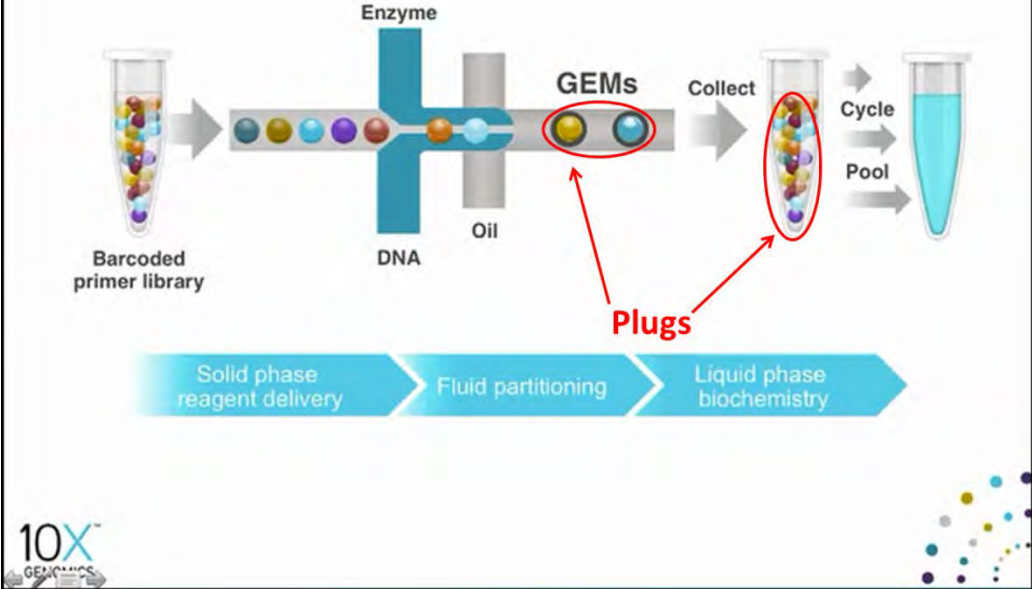
	'091 Claim Language	Infringement Support
		<p><i>cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p>  <ul style="list-style-type: none"> <li>• The amplified DNA product is soluble in the aqueous droplets.</li> </ul>
091-53	53. The method of claim 37, further comprising employing a number of devices in parallel.	<p><b><u>10X’s GemCode platform uses microfluidic chips with eight channels in parallel allowing for eight samples to be tested in parallel.</u></b></p> <ul style="list-style-type: none"> <li>• As Dr. Schnall Levin explained during his August 2015 webinar, below is a “cross-</li> </ul>

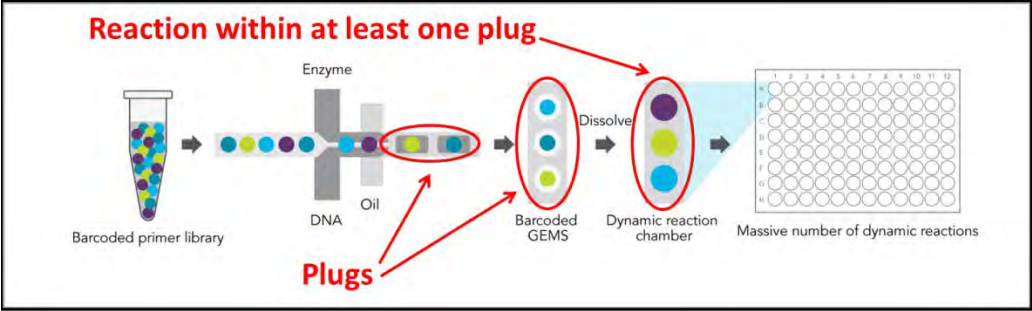
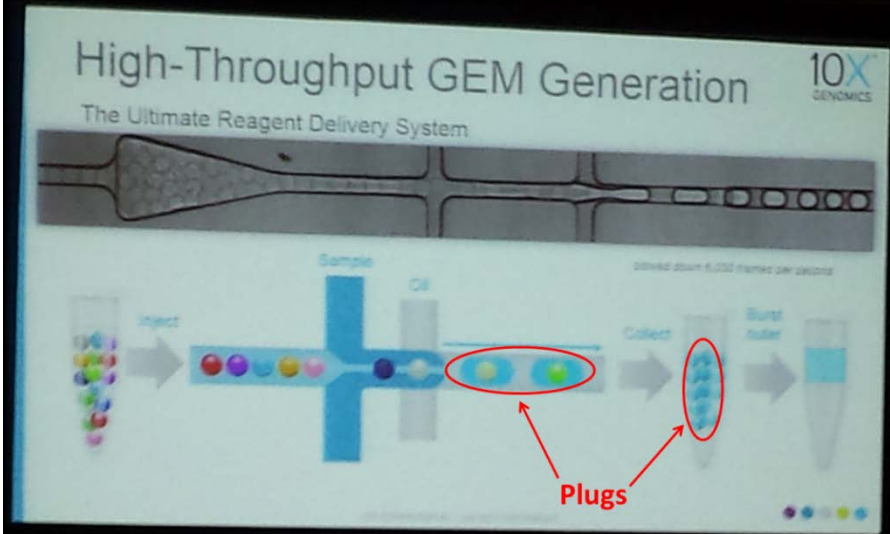
	'091 Claim Language	Infringement Support
		<p>section of one of the channels present in [10X's] microfluidic chip. <i>If you look at one of our microfluidic chips there would be eight of these channels in parallel such that you can run eight samples at a time.</i>" <i>Id.</i> at 9:32-47.</p> 
091-56	56. The method of claim 37, wherein the volume of at least one plug is about 1 femtoliter to about 250 nL.	<p><b><u>10X's droplets have a volume between 1 femtoliters and about 250 nanoliters.</u></b></p> <ul style="list-style-type: none"> <li>At the 2016 AGBT conference, 10X provided a workshop in which it described its technology. The figure below from 10X's workshop presentation depicts in Panel J a droplet alongside a "Singe T Cell." Based on the fact that a T cell is roughly 10 <math>\mu\text{m}</math> in</li> </ul>

	'091 Claim Language	Infringement Support
		<p>diameter, 10X's droplets are roughly 100 <math>\mu\text{m}</math> in diameter. This leads to a droplet volume in 10X's GemCode platform of roughly 0.5 nanoliters, which is between two femtoliters and one hundred nanoliters.</p> <p>Ex. 41 [Core Genomics] at 4.</p>
091-57a	57. A method of conducting a reaction within at least one plug comprising the steps of:	<p>10X's GemCode platform uses "method of conducting a reaction within at least one plug."</p> <ul style="list-style-type: none"> <li>• The plugs are microfluidic droplets that are formed in 10X's GemCode platform.</li> <li>• A reaction that is conducted in the plug is a DNA amplification reaction.</li> </ul>

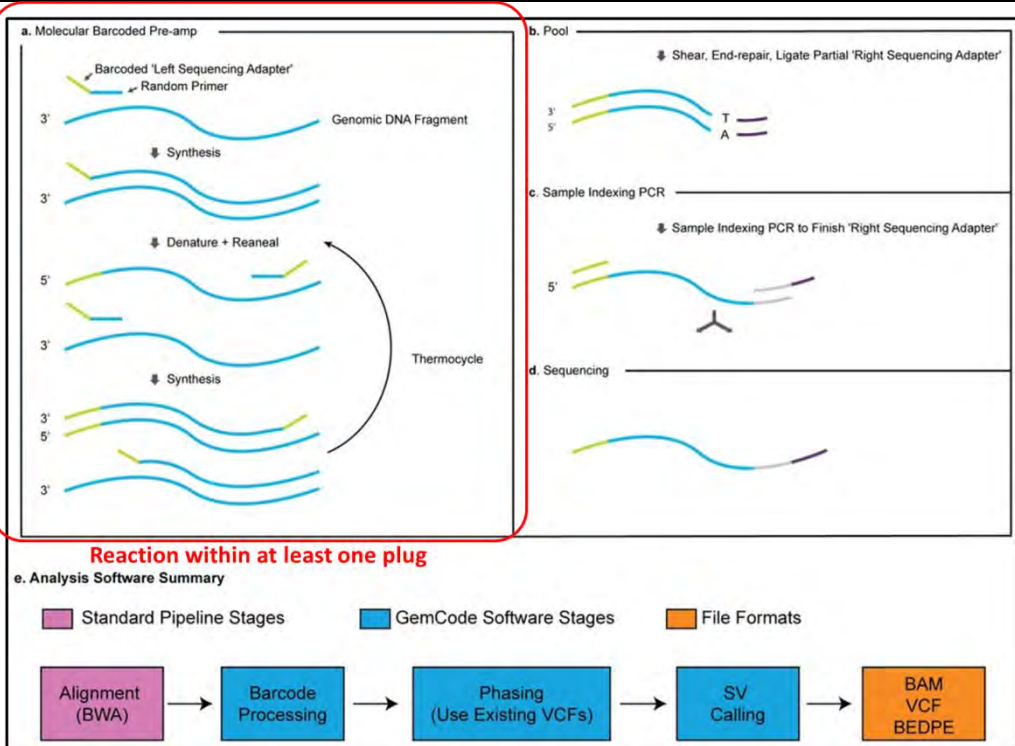
	'091 Claim Language	Infringement Support
		<p><b><u>10X's GemCode platform is a microfluidic system using "plugs," which 10X refers to as droplets or "GEMs".</u></b></p> <ul style="list-style-type: none"> <li>• The '091 patent's description of "plugs" includes the following: "'Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 11 ['091 patent] at 9:20-23.</li> <li>• On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '091 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>" <i>Id.</i> at 9:48-10:39.</li> </ul>



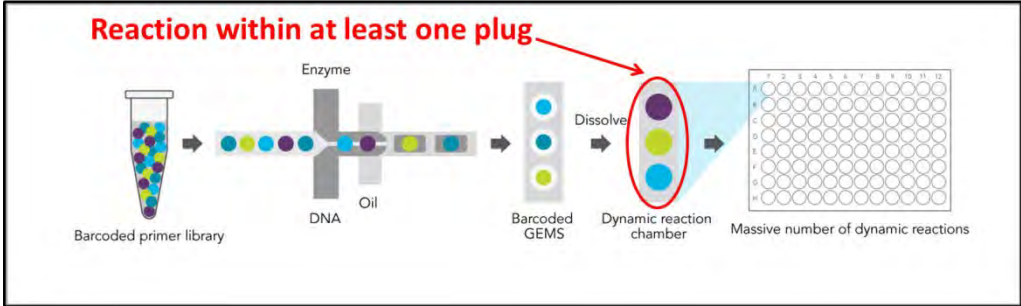
	'091 Claim Language	Infringement Support
		<p data-bbox="846 316 1633 358">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <ul style="list-style-type: none"> <li data-bbox="743 1081 1898 1260">10x's website is consistent with Dr. Schnall-Levin's description of 10X's Platform. 10X's website states that "[t]he instrument features precise <i>microfluidics</i> coupled with single button, user-friendly operation." Ex. 39 [10X Website Excerpts] at 3. The website further states that the 10X chip kit "[c]ontains the <i>microfluidic chips</i> and accessories required for sample partitioning." <i>Id.</i> at 5.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p><b>Reaction within at least one plug</b></p> <p>Barcoded primer library</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>Barcoded GEMS</p> <p>Dissolve</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> <p><b>Plugs</b></p> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul>  <p>High-Throughput GEM Generation</p> <p>The Ultimate Reagent Delivery System</p> <p>10X GENOMICS</p> <p>Sample</p> <p>Oil</p> <p>Inject</p> <p>Collect</p> <p>Burst outlet</p> <p><b>Plugs</b></p>

	'091 Claim Language	Infringement Support
		<p>Ex. 37 [JP Morgan presentation] at 2.</p> <p><b><u>10X's GemCode platform conducts DNA amplification reactions within the microfluidic droplets ("plugs")</u></b></p> <ul style="list-style-type: none"> <li>• The slide above from 10X's August 2015 presentation is entitled "&gt;100,000 <i>Reactions</i> Assembled in &lt;5 min," which demonstrates that reactions are occurring within the microfluidic droplets.</li> <li>• The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp," which is taken from 10X's recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X's platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the GemCode sequencing workflow. Stage (a) 'Molecular Barcoded Pre-amp' shows a genomic DNA fragment being amplified with a barcoded left sequencing adapter and a random primer. Stage (b) 'Pool' shows the DNA being sheared, end-repaired, and ligated with a partial right sequencing adapter. Stage (c) 'Sample Indexing PCR' shows the completion of the right sequencing adapter. Stage (d) 'Sequencing' shows the final DNA molecule. Stage (e) 'Analysis Software Summary' shows the workflow from Alignment (BWA) to Barcode Processing, Phasing (Use Existing VCFs), SV Calling, and finally BAM VCF BEDPE file formats.</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <b>amplify the DNA</b> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry</li> </ul>

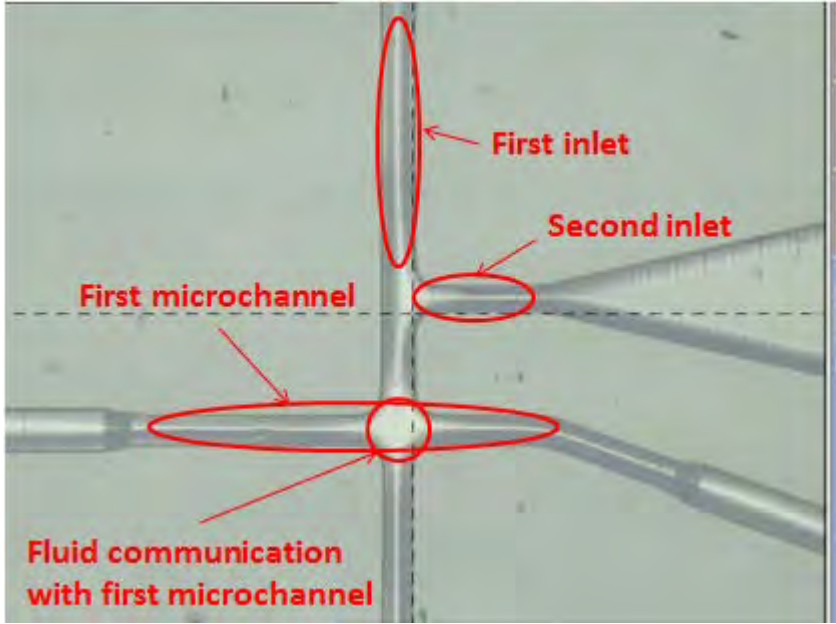
	'091 Claim Language	Infringement Support
		<p>that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 552 1759 1276"> <p>The diagram illustrates the process of low-input molecular barcoding in GEMs. It is divided into four numbered steps:</p> <ol style="list-style-type: none"> <li><b>1 Molecular barcoding in GEMs:</b> This step is highlighted with a red box. It shows a long blue line representing a genomic template with several small blue and yellow segments (oligos) attached. A circular arrow labeled 'Cycle' indicates a thermal cycling process. To the right, a test tube contains many small, multi-colored droplets representing GEMs.</li> <li><b>2 Pool, Ligate right adapter:</b> This step shows a test tube with a blue liquid. Below it, a blue line with yellow segments is shown next to two small white adapters labeled 'T' and 'A'. The text 'Shear, End-repair, A-tail, Ligate' is present.</li> <li><b>3 Sample Indexing PCR:</b> This step shows a blue line with yellow segments and a small purple segment, representing the addition of a sample-specific index.</li> <li><b>4 Sequence and Analyze:</b> This step shows the final product, a blue line with yellow and purple segments, ready for sequencing.</li> </ol> <p>The 10X Genomics logo is located at the bottom left of the diagram.</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x's website depicts the microfluidic system wherein plugs are received in a "dynamic reaction chamber" wherein a "massive number of dynamic reactions" occur.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>Ex. 39 [10X Website Excerpts] at 1.</p>
091-57b	introducing a carrier-fluid into a first microchannel of a device;	<p>10X's GemCode platform introduces "a carrier-fluid into a first microchannel of a device."</p> <ul style="list-style-type: none"> <li>• The carrier fluid is the oil that is used in 10X's microfluidic device.</li> <li>• The first microchannel is the channel through which the stream of oil is introduced perpendicularly into a stream of aqueous fluid that is packaged into droplets.</li> </ul> <p><b><u>10X's GemCode platform introduces an oil ("carrier fluid") into a first channel of a microfluidic chip.</u></b></p> <ul style="list-style-type: none"> <li>• During his August webinar, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the <i>channel in our microfluidic chip.</i>" <i>Id.</i> at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And <i>on the third input well the user puts in the oil provided again by 10X.</i> There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" <i>Id.</i> at 9:48-10:39. Thus, the channel containing the oil (which is a "carrier fluid immiscible with the aqueous</li> </ul>

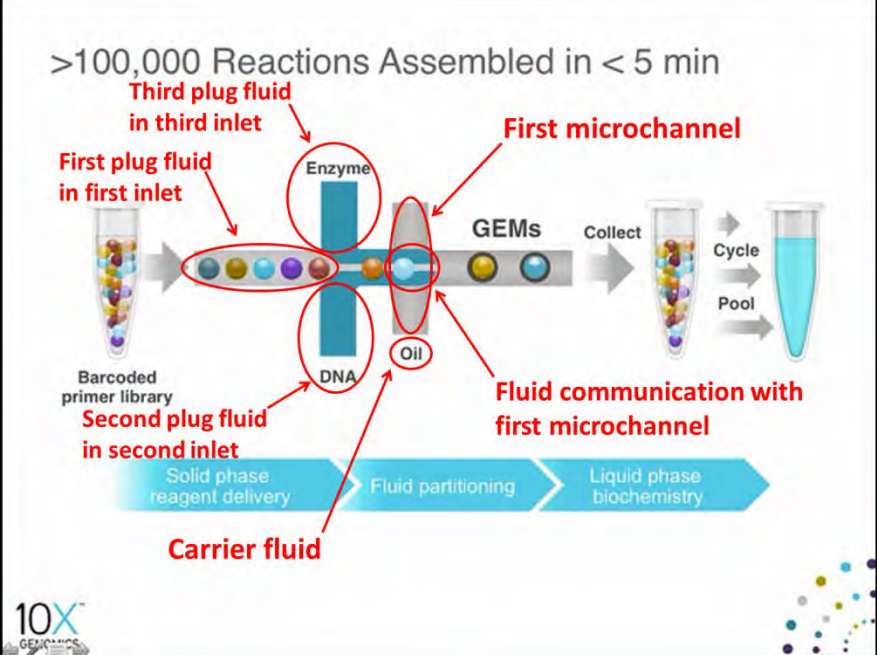
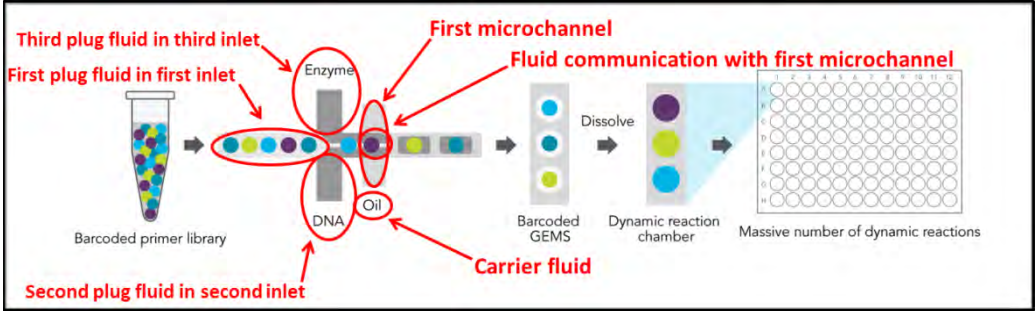
	'091 Claim Language	Infringement Support
		<p>solutions”) intersects and flows into the channel containing the aqueous solution of the gel beads, biochemical reagents and DNA.</p> <div data-bbox="793 370 1667 1029"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div> <ul style="list-style-type: none"> <li>• In the figure above the channel containing the continuously flowing oil is shown in grey.</li> <li>• The figure below from 10x’s website further notes the continuously flowing oil from a second channel shown in light grey.</li> </ul>

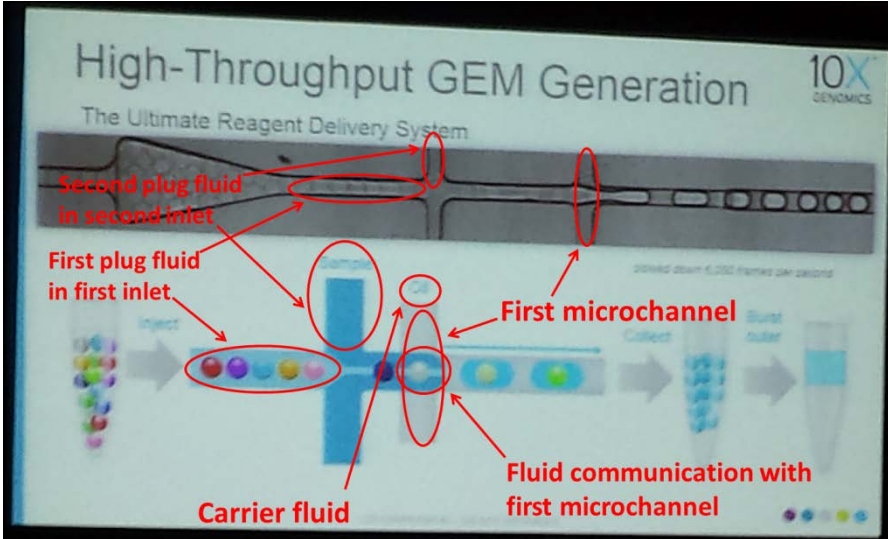


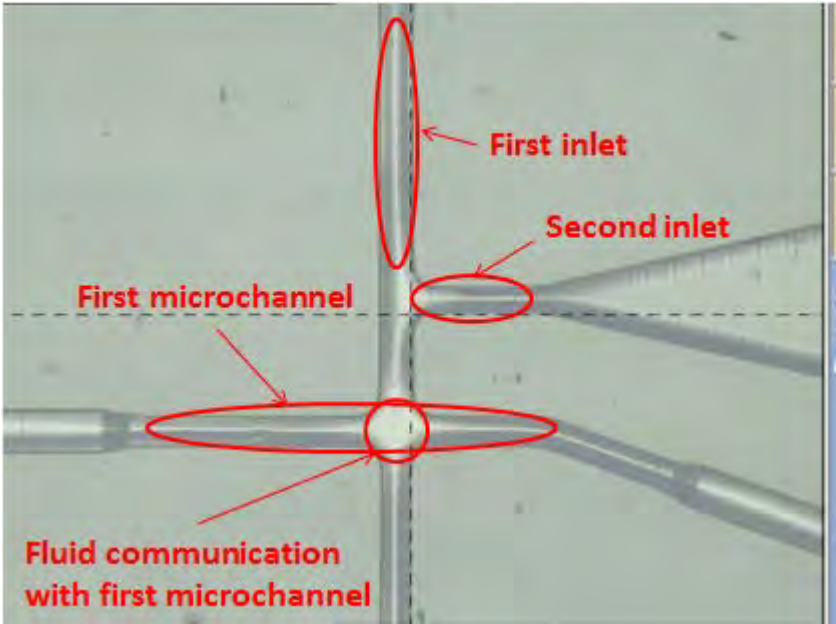
	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1669 527"> <p>Barcoded primer library</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>Carrier fluid</p> <p>First microchannel</p> <p>Dissolve</p> <p>Barcoded GEMS</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> </div> <p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which an oil is shown flowing into a channel of the microfluidic chip in light grey:</li> </ul> <div data-bbox="787 755 1669 1291"> <p>High-Throughput GEM Generation</p> <p>The Ultimate Reagent Delivery System</p> <p>10X GENOMICS</p> <p>Carrier fluid</p> <p>Sample</p> <p>First microchannel</p> <p>Inject</p> <p>Collect</p> <p>Wash</p> </div> <p>Ex. 37 [JP Morgan presentation] at 2.</p>

	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. The carrier fluid is introduced into what is labeled "first microchannel."</li> </ul> 
091-57c	introducing a stream of a first plug-fluid into a first	10X's GemCode platform introduces "a stream of a first plug-fluid into a first inlet in fluid communication with the first microchannel and simultaneously introducing a stream of a

	'091 Claim Language	Infringement Support
	<p>inlet in fluid communication with the first microchannel and simultaneously introducing a stream of a second plug-fluid into a second inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier fluid at a junction area of the first and second inlets and the first microchannel; wherein:</p>	<p>second plug-fluid into a second inlet in fluid communication with the first microchannel so that at least one plug forms in the carrier-fluid after the first and second plug-fluids contact The carrier fluid”</p> <ul style="list-style-type: none"> <li>• There are at least three streams of aqueous fluid in 10X’s product: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads. Any two of these fluids may be chosen as the first and second plug fluid. The designations of the first, second, and third fluids in the figures in this chart are arbitrary.</li> <li>• Each of these three plug fluids are introduced via their own inlet. They combine at another inlet that perpendicularly intersects (and is hence in fluid communication with) the first microchannel that carries the oil carrier fluid.</li> <li>• The plugs are the droplets (which 10X sometimes refer to as GEMs) that form at the junction between the inlet and the carrier fluid stream.</li> </ul> <p><b><u>10X’s GemCode platform simultaneously introduces at least two streams of plug fluid via at least two inlets</u></b></p> <ul style="list-style-type: none"> <li>• During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the channels in our microfluidic chip.” Ex. 4 [10X Webinar] at 9:33-39. “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads.</i> This is a reagent delivered by 10x. <i>On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly.</i> They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.” <i>Id.</i> at 9:48-10:39. Thus, two streams of plug-fluids, the first containing biochemical reagents and DNA, and the second containing an aqueous solution of the gel beads, are introduced into the same central inlet channel.</li> </ul>

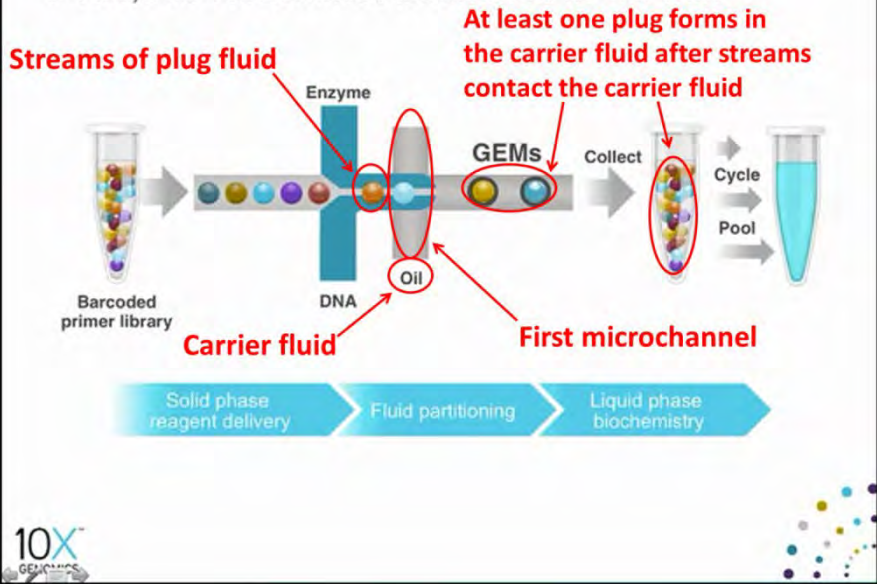
	'091 Claim Language	Infringement Support
		 <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>First plug fluid in first inlet</p> <p>Third plug fluid in third inlet</p> <p>Enzyme</p> <p>First microchannel</p> <p>GEMs</p> <p>Collect</p> <p>Cycle</p> <p>Pool</p> <p>Barcoded primer library</p> <p>DNA</p> <p>Oil</p> <p>Fluid communication with first microchannel</p> <p>Second plug fluid in second inlet</p> <p>Solid phase reagent delivery</p> <p>Fluid partitioning</p> <p>Liquid phase biochemistry</p> <p>Carrier fluid</p> <p>10x GENOMICS</p> <ul style="list-style-type: none"> <li>The figure below from 10x's website further notes the introduction of two streams through a central channel.</li> </ul>  <p>Third plug fluid in third inlet</p> <p>First plug fluid in first inlet</p> <p>Enzyme</p> <p>First microchannel</p> <p>Fluid communication with first microchannel</p> <p>Dissolve</p> <p>Barcoded GEMS</p> <p>Dynamic reaction chamber</p> <p>Massive number of dynamic reactions</p> <p>Barcoded primer library</p> <p>DNA</p> <p>Oil</p> <p>Carrier fluid</p> <p>Second plug fluid in second inlet</p>

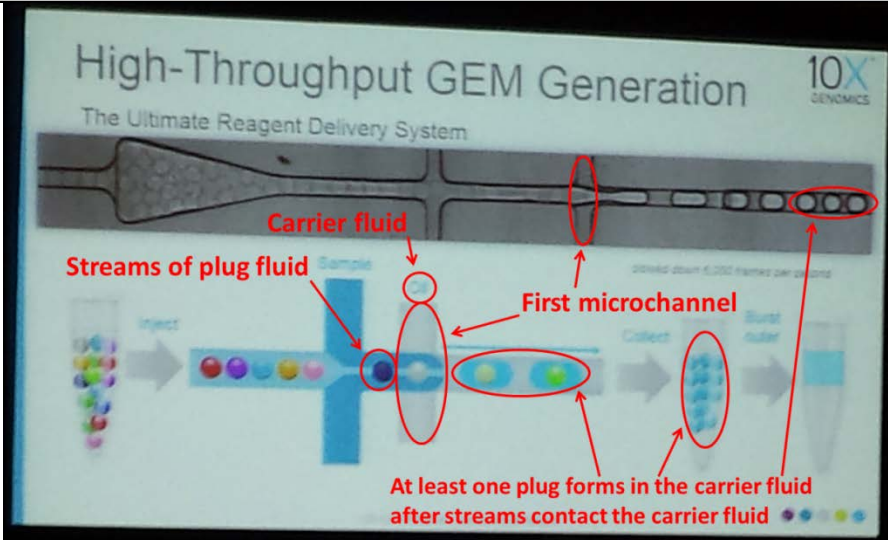
	'091 Claim Language	Infringement Support
		<p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which two streams are introduced to a middle inlet channel.</li> </ul>  <p>Ex. 37 [JP Morgan presentation] at 2.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first stream of plug fluid is introduced into</li> </ul>

	'091 Claim Language	Infringement Support
		<p>what is labeled as the “first inlet” and a second stream of plug fluid is introduced into the “second inlet.” The first and second streams of plug fluid are in “fluid communication with the first microchannel.”</p>  <p><b><u>The three inlets are in fluid communication with the first channel containing the oil (“carrier-fluid”) such that droplets (“plugs”) form in the oil after the first and second streams of plug fluid contact the oil</u></b></p> <ul style="list-style-type: none"> <li>• The '091 patent’s description of “plugs” includes the following: “‘Plugs’ in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible.” Ex. 11 [’091 patent] at 9:20-23.</li> </ul>

	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '193 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b>" <i>Id.</i> at 9:48-10:39.</li> </ul>

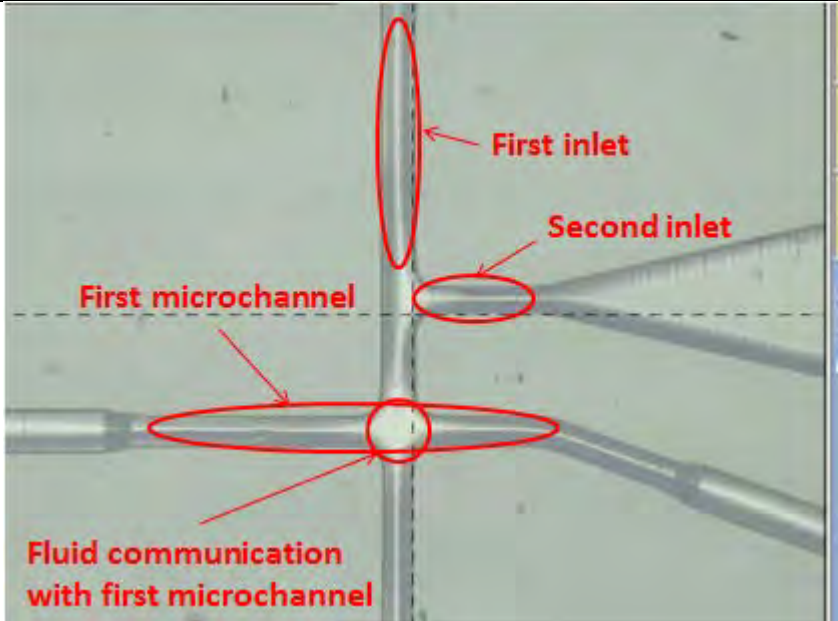


	'091 Claim Language	Infringement Support
		<p data-bbox="848 305 1520 342">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p>The diagram illustrates the 10x Genomics microfluidic process. It starts with a 'Barcoded primer library' (represented by a vial of colored beads) and 'DNA' (represented by a blue line). These are combined in a 'First microchannel' where 'Streams of plug fluid' (colored beads) and 'Carrier fluid' (blue line) intersect. This process is labeled 'Solid phase reagent delivery'. The resulting droplets, containing 'GEMs' (Genomic Element Microfluidic) and 'Oil', are then 'Collected' into a vial. This step is labeled 'Fluid partitioning'. The final step is 'Liquid phase biochemistry', where the droplets are 'Cycled' and 'Pooled' into a larger vial. The diagram also includes a '10x Genomics' logo and a micrograph of the actual microfluidic device showing the droplets as light gray circles in the rightmost channel.</p> <p data-bbox="806 380 1079 417">Streams of plug fluid</p> <p data-bbox="1100 417 1163 438">Enzyme</p> <p data-bbox="1247 342 1604 438">At least one plug forms in the carrier fluid after streams contact the carrier fluid</p> <p data-bbox="1268 477 1352 498">GEMs</p> <p data-bbox="1373 477 1436 498">Collect</p> <p data-bbox="1499 498 1562 519">Cycle</p> <p data-bbox="1499 558 1562 579">Pool</p> <p data-bbox="848 639 974 660">Barcoded primer library</p> <p data-bbox="1121 623 1163 644">DNA</p> <p data-bbox="1184 591 1226 612">Oil</p> <p data-bbox="974 660 1142 682">Carrier fluid</p> <p data-bbox="1310 660 1562 682">First microchannel</p> <p data-bbox="953 721 1100 742">Solid phase reagent delivery</p> <p data-bbox="1163 737 1310 758">Fluid partitioning</p> <p data-bbox="1373 721 1499 742">Liquid phase biochemistry</p> <p data-bbox="806 850 890 915">10x GENOMICS</p> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows that plugs are formed after the two inlet streams of plug fluid intersect the oil, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the rightmost channel.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan presentation] at 2.</p>
091-57d	-a first plug-fluid comprises a first reagent;	<p>10X's GemCode platform has a first plug fluid that comprises a first reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the first plug fluid comprising a first reagent. The designations of the first plug fluid, second plug fluid, and third plug fluid in this chart are arbitrary.</li> </ul> <p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more</u></b></p>

	'091 Claim Language	Infringement Support
		<p><b><u>reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the channels in our microfluidic chip.” Ex. 4 [10X Webinar] at 9:33-39. “If you look starting from left to right what you see is the channels that are from three different input wells. <b><i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i></b> And on the third input well the user puts in the oil provided again by 10X. There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.” <i>Id.</i> at 9:48-10:39.</li> </ul>

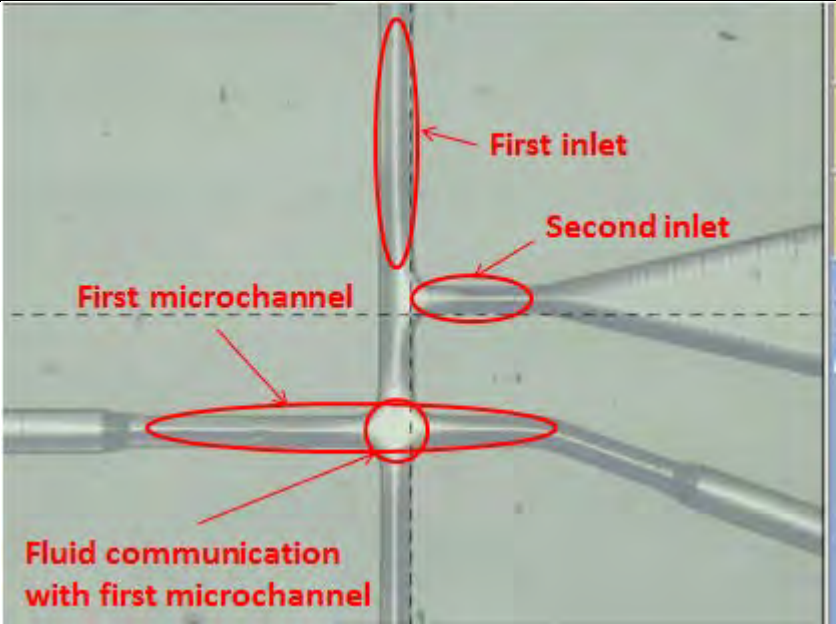
	'091 Claim Language	Infringement Support
		<div data-bbox="791 261 1671 927"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> <p>Barcoded primer library</p> <p>First plug fluid</p> <p>Third plug fluid</p> <p>Enzyme</p> <p>DNA</p> <p>Oil</p> <p>GEMs</p> <p>Collect</p> <p>Cycle</p> <p>Pool</p> <p>Second plug fluid</p> <p>Solid phase reagent delivery</p> <p>Fluid partitioning</p> <p>Liquid phase biochemistry</p> <p>10X GENOMICS</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A first stream of plug fluid is introduced into what is labeled as the "first inlet" and is comprised of one or more reagents.</li> </ul>

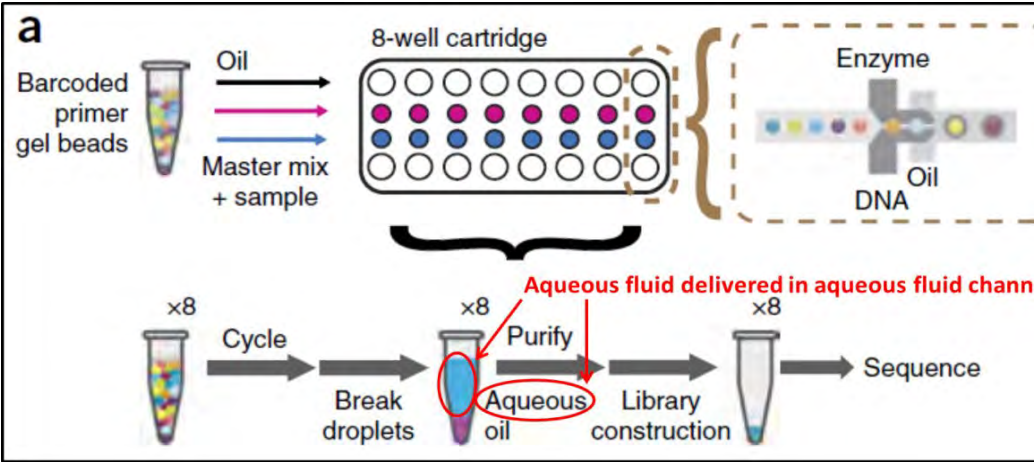
	'091 Claim Language	Infringement Support
		
091-57e	-a second plug-fluid comprises a second reagent;	<p>10X's GemCode platform has a second plug fluid that comprises a second reagent.</p> <ul style="list-style-type: none"> <li>• There are at least three streams of plug fluid in 10X's product that each contains one or more reagents: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers.</li> <li>• The sample DNA is a substrate for a DNA amplification reaction. The enzyme is a reagent that catalyzes the amplification reaction, and is delivered with other reagents (e.g, nucleotides) that are used in the amplification reaction. The gel beads deliver primers that are used in the amplification reaction.</li> <li>• Any one of plug fluids comprising reagents may be designated as the second plug fluid comprising a second reagent, consistent with the choice that is made for the first plug fluid and reagent. The designations of the first plug fluid, second plug fluid, and third</li> </ul>

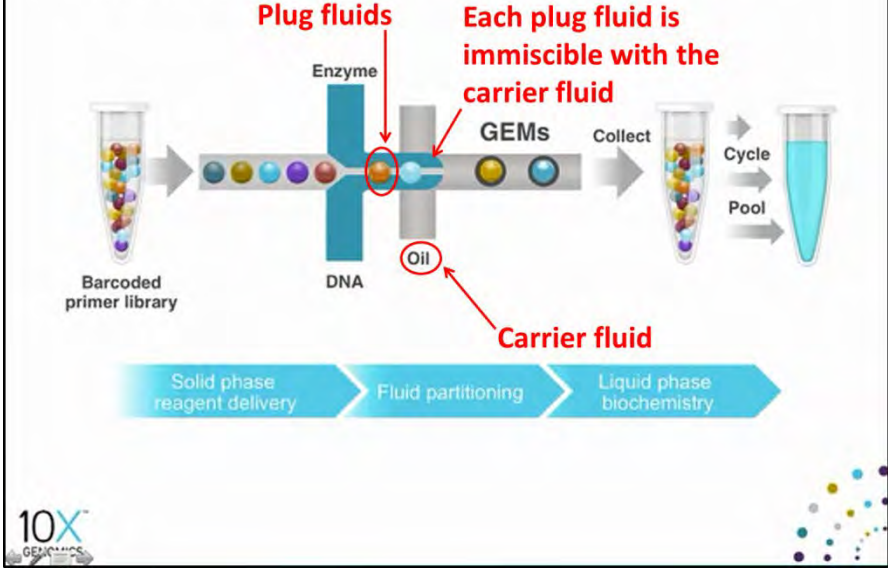
	'091 Claim Language	Infringement Support
		<p>plug fluid in this chart are arbitrary.</p> <p><b><u>10X's GemCode platform has at least three aqueous fluids that each contain one or more reagents.</u></b></p> <ul style="list-style-type: none"> <li>During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead." <i>Id.</i> at 9:48-10:39.</li> </ul>

	'091 Claim Language	Infringement Support
		<div data-bbox="793 264 1669 925"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same "second inlet." This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. A second stream of plug fluid is introduced into what is labeled as the "second inlet" and is comprised of one or more reagents.</li> </ul>

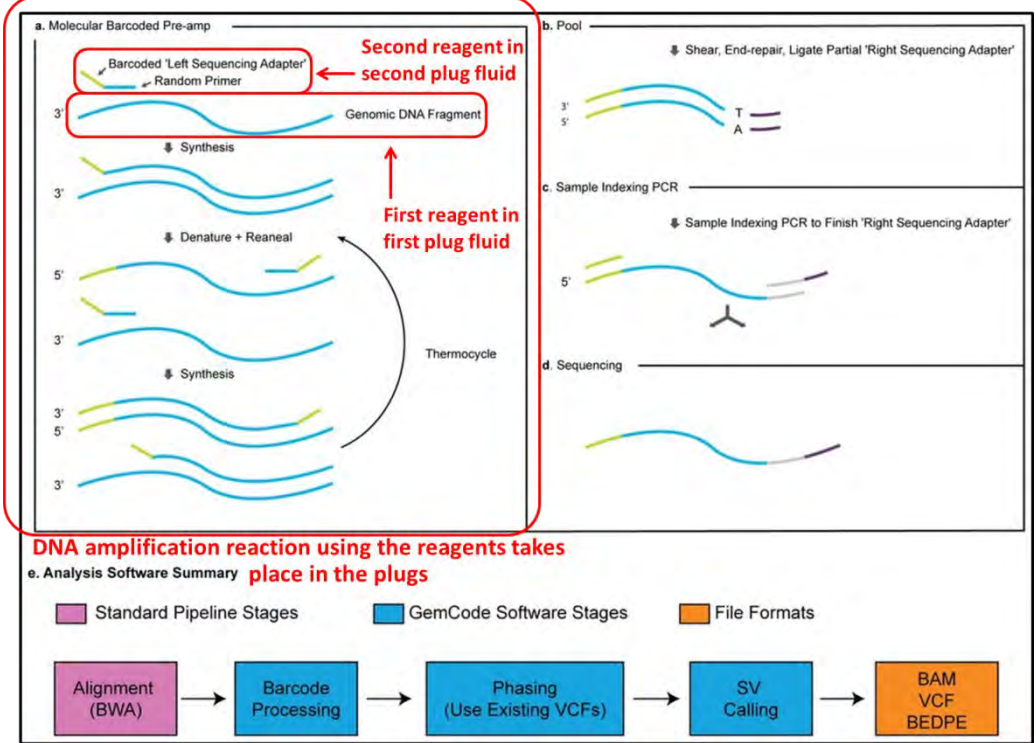


	'091 Claim Language	Infringement Support
		
091-57f	-each plug-fluid is immiscible with the carrier-fluid;	<p><b><u>The three plug fluids in 10X's GemCode platform are aqueous and hence immiscible with the oil carrier fluid.</u></b></p> <ul style="list-style-type: none"> <li>In 10x's GemCode platform the channels that carry the enzyme, DNA, and barcoded gelbeads for packaging into droplets are aqueous fluid channels. This is shown in 10X's recent <i>Nature Biotechnology</i> paper, which describes the operation of 10X's GemCode platform. As explained in this paper, "[t]he first junction combines a close-packed <b>aqueous</b> slurry of gel beads with the sample and reagent mixture, and the second junction delivers the oil-surfactant solution." Ex. 5 [<i>Nature Biotechnology</i>] at 2. The droplets that are formed in 10X's microfluidic device are broken after a DNA amplification reaction is carried out inside the droplet. The fluid that is inside the droplets separates from the oil that originally surrounded and carried the droplets. As depicted below, the interior of the droplet is "Aqueous" and is shown in blue. Thus,</li> </ul>

	'091 Claim Language	Infringement Support
		<p>the channels that provided the fluids for the interior of the droplets are aqueous fluid channels.</p>  <p>Ex. 5 [<i>Nature Biotechnology</i>] at Fig. 1a.</p> <ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '091 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>

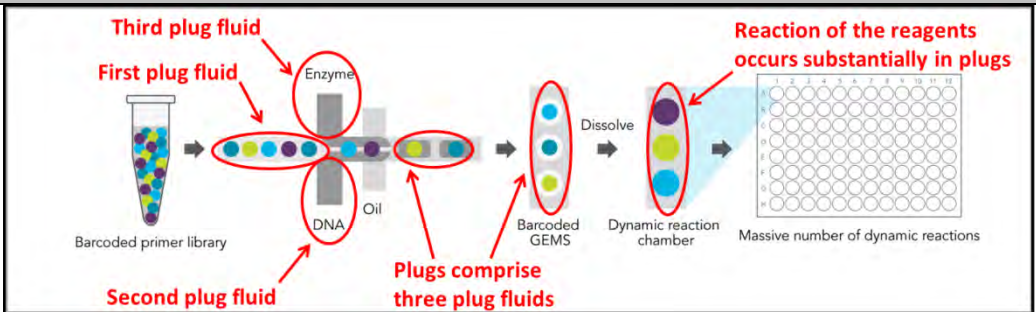
	'091 Claim Language	Infringement Support
		<p data-bbox="835 305 1514 342">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <p data-bbox="1039 365 1186 397">Plug fluids</p> <p data-bbox="1249 365 1501 479">Each plug fluid is immiscible with the carrier fluid</p> <p data-bbox="1102 430 1165 462">Enzyme</p> <p data-bbox="1102 641 1165 673">DNA</p> <p data-bbox="1270 495 1333 527">GEMs</p> <p data-bbox="1375 495 1438 527">Collect</p> <p data-bbox="1501 511 1564 544">Cycle</p> <p data-bbox="1501 560 1564 592">Pool</p> <p data-bbox="850 641 976 673">Barcoded primer library</p> <p data-bbox="1186 609 1228 641">Oil</p> <p data-bbox="1270 690 1438 722">Carrier fluid</p> <p data-bbox="934 738 1144 771">Solid phase reagent delivery</p> <p data-bbox="1165 738 1333 771">Fluid partitioning</p> <p data-bbox="1375 738 1564 771">Liquid phase biochemistry</p> <p data-bbox="808 868 871 917">10X GENOMICS</p> <ul data-bbox="693 974 1900 1047" style="list-style-type: none"> <li>As shown in the above image, the blue fluid and colored gel beads are immiscible with the oil because the intersection forms isolated droplets rather than a homogenous liquid.</li> </ul>
091-57g	-each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug; and	<p data-bbox="693 1084 1900 1157">In 10X's GemCode platform "each plug comprises both the first and second plug-fluids so that the reaction of the reagents substantially occurs in the plug."</p> <ul data-bbox="745 1198 1900 1419" style="list-style-type: none"> <li>There are at least three streams of plug fluid in 10X's GemCode platform: (1) the aqueous fluid containing the sample DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads, which deliver primers. All of these plug fluids are packaged into droplets, and any two of these plug fluids may be selected as the first and second plug fluid.</li> <li>The reaction that occurs in the droplets using the reagents contained in the plug fluids</li> </ul>

	'091 Claim Language	Infringement Support
		<p>is a DNA amplification reaction.</p> <p><b><u>The microfluidic droplets (“plugs”) in 10X’s GemCode platform comprise all three of the plug fluids that are used in 10X’s product.</u></b></p> <ul style="list-style-type: none"> <li>During his August 2015 presentation, Dr. Schnall-Levin explained that each droplet contains a small portion of the DNA from the user and a gel bead: “If you look starting from left to right what you see is the channels that are from three different input wells. <i>On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA.</i> And on the third input well the user puts in the oil provided again by 10X. <i>There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>” Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul> <p><b><u>10X’s GemCode platform conducts DNA amplification reactions within the microfluidic droplets (“plugs”) using the reagents from the first and second plug fluids</u></b></p> <ul style="list-style-type: none"> <li>The reactions which take place within the microfluidic droplets is depicted in the figure below in the panel labeled “a. Molecular Barcoded Pre-amp,” which is taken from 10X’s recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X’s platform. The figure below shows a single stranded “Genomic DNA Fragment” that is extended through the use of a “Random Primer.” The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>The diagram illustrates the GemCode sequencing process in five stages:</p> <ul style="list-style-type: none"> <li><b>a. Molecular Barcoded Pre-amp:</b> A genomic DNA fragment is amplified using a barcoded left sequencing adapter and a random primer. The process involves synthesis, denature + reanneal, and another synthesis step, occurring in a thermocycle. Red annotations highlight the 'Second reagent in second plug fluid' (the barcoded adapter) and the 'First reagent in first plug fluid' (the random primer).</li> <li><b>b. Pool:</b> The DNA fragments are pooled and sheared, end-repaired, and ligated with a partial right sequencing adapter.</li> <li><b>c. Sample Indexing PCR:</b> The pooled DNA is amplified using sample indexing PCR to finish the right sequencing adapter.</li> <li><b>d. Sequencing:</b> The indexed DNA is sequenced.</li> <li><b>e. Analysis Software Summary:</b> A flowchart showing the analysis pipeline: Alignment (BWA) → Barcode Processing → Phasing (Use Existing VCFs) → SV Calling → BAM VCF BEDPE. The legend indicates that pink boxes represent Standard Pipeline Stages, blue boxes represent GemCode Software Stages, and orange boxes represent File Formats.</li> </ul> <p>Red text annotations on the diagram state: "DNA amplification reaction using the reagents takes place in the plugs".</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <i>amplify the DNA</i> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry</li> </ul>

	'091 Claim Language	Infringement Support
		<p>that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="787 552 1669 1209"> <p>The diagram illustrates the process of low-input molecular barcoding in GEMs. It is divided into four numbered steps:</p> <ol style="list-style-type: none"> <li><b>1 Molecular barcoding in GEMs</b>: A red box highlights this step, with a red arrow pointing to it from the text "Reaction of reagents occurs substantially in plugs". The diagram shows a blue tube (plug) with a red arrow indicating the "First reagent from first plug fluid" and a blue arrow indicating the "Second reagent in second plug fluid". A circular arrow labeled "Cycle" is shown next to a test tube.</li> <li><b>2 Pool, Ligate right adapter</b>: The diagram shows a blue tube being sheared, end-repaired, A-tailed, and ligated with a T and A adapter.</li> <li><b>3 Sample Indexing PCR</b>: The diagram shows a blue tube with a red arrow indicating the "First reagent from first plug fluid" and a blue arrow indicating the "Second reagent in second plug fluid".</li> <li><b>4 Sequence and Analyze</b>: The diagram shows a blue tube with a red arrow indicating the "First reagent from first plug fluid" and a blue arrow indicating the "Second reagent in second plug fluid".</li> </ol> <p>The 10X Genomics logo is visible in the bottom left corner of the diagram.</p> </div> <ul style="list-style-type: none"> <li>The figure below from 10x's website depicts the microfluidic system wherein plugs are received in a "dynamic reaction chamber" wherein a "massive number of dynamic reactions" occur.</li> </ul>

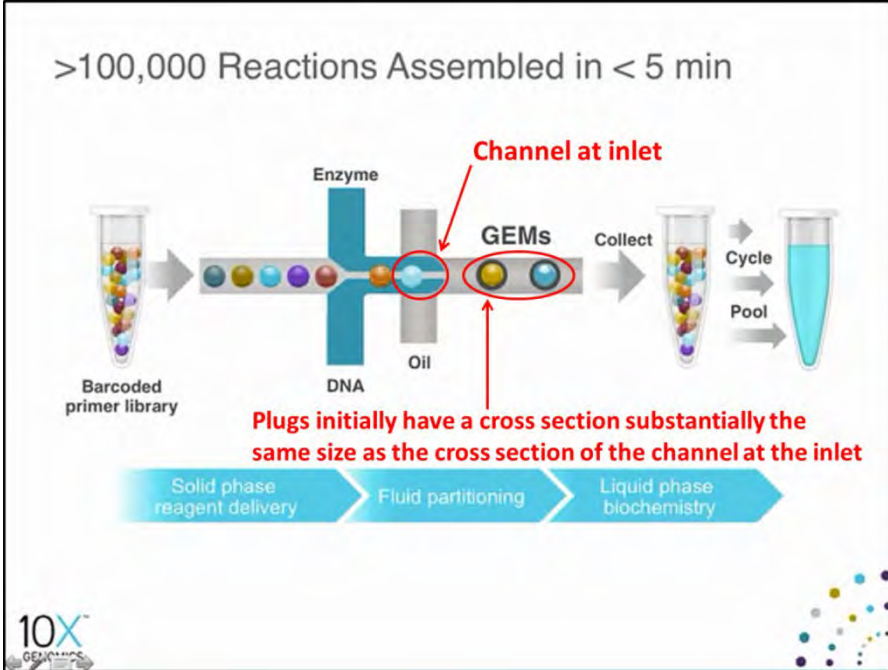


	'091 Claim Language	Infringement Support
		 <p>Ex. 4 [10X Webinar] at 1.</p>
091-57h	-each plug is substantially surrounded by carrier.	<p><b><u>10X's GemCode platform forms microfluidic droplets ("plugs") such that the droplets are substantially surrounded by the oil.</u></b></p> <ul style="list-style-type: none"> <li>The '091 patent's description of "plugs" includes the following: "Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 11 ['091 patent] at 9:20-23.</li> <li>During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the same manner as the '091 patent. The process is depicted in the figure below. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" Ex. 4 [Webinar] at 9:48-10:39.</li> </ul>

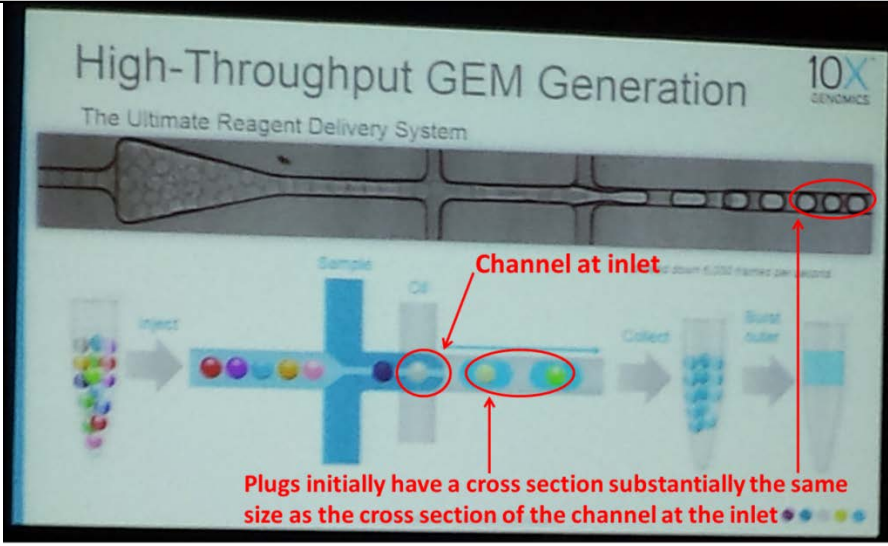


	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1669 933"> <p>The diagram illustrates the 10X Genomics GemCode system. It shows a microfluidic process where a 'Barcoded primer library' and 'DNA' are combined with an 'Enzyme' to form 'GEMs' (droplets). These GEMs are then 'Collected' and undergo 'Cycle' and 'Pool' steps. A red circle highlights the 'Oil' component, which is the 'Carrier fluid'. A red arrow points to the GEMs with the text 'Plugs substantially surrounded by carrier fluid'. A blue arrow at the bottom indicates the process flow: 'Solid phase reagent delivery' → 'Fluid partitioning' → 'Liquid phase biochemistry'. The 10X Genomics logo is in the bottom left corner.</p> </div> <ul style="list-style-type: none"> <li>As shown in the image above, each microfluidic droplet or plug is called a “GEM” and is substantially surrounded by the grey oil, which is the carrier fluid.</li> </ul> <p>The partitioning of DNA into droplets by 10X’s GemCode system according to the foregoing methods is also established by other resources. For instance, 10x’s website states “The 10X Genomics reagent delivery system randomly partitions DNA fragments, then prepares sequencing libraries in parallel such that all molecules produced within a partition share a unique, partition-specific barcode.” Ex. 39 [10x Website Excerpts] at 1. The website further states that the 10x chip kit “[c]ontains the microfluidic chips and accessories required for <i>sample partitioning</i>.” <i>Id.</i> at 5. 10x’s website further shows the formation of the claimed plugs:</p>

	'091 Claim Language	Infringement Support
		<div data-bbox="787 261 1812 570" data-label="Diagram"> </div> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10x Technologies' JP Morgan presentation further shows the plugs emerging from the junction of the oil (shown in gray) and the aqueous fluid containing the reagents (shown in blue):</li> </ul> <div data-bbox="787 824 1671 1365" data-label="Image"> </div>

	'091 Claim Language	Infringement Support
		Ex. 37 [JP Morgan presentation] at 2.
091-58	58. The method of claim 57, wherein each plug initially has a cross section that is substantially the same size as the cross section of the channel at the junction area.	<p><b><u>The microfluidic droplets in 10X's GemCode platform initially have a cross section that is substantially the same size as the cross section of the channel containing the aqueous fluids.</u></b></p> <ul style="list-style-type: none"> <li>During his August webinar, Dr. Schnall-Levin explained that the picture below is “a cross-section of one of the <i>channel in our microfluidic chip</i>.” <i>Id.</i> at 9:33-39. In that picture, each plug labeled GEMs has a cross section substantially the same size as the cross section as the cross section of the center channel.</li> </ul> 

	'091 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10x's website is also consistent in showing that the cross section of the plug is initially substantially the same size as the cross section of the center channel.</li> </ul> <div data-bbox="787 371 1814 683"> <p>Channel at inlet</p> <p>Plugs initially have a cross section substantially the same size as the cross section of the channel at the inlet</p> </div> <ul style="list-style-type: none"> <li>10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles and initially have a cross section that is substantially the same as the cross section of the center channel.</li> </ul>

	'091 Claim Language	Infringement Support
		 <p>High-Throughput GEM Generation The Ultimate Reagent Delivery System 10X GENOMICS</p> <p>Channel at inlet</p> <p>Plugs initially have a cross section substantially the same size as the cross section of the channel at the inlet</p> <p>Inject, Sample, Oil, Collect, Burst, Bubble</p>

Ex. 37 [JP Morgan presentation] at 2.

# EXHIBIT 18

**Infringement of U.S. Patent No. 8,304,193 by 10X's GemCode Platform<sup>1</sup>**

	<b>'193 Claim Language</b>	<b>Infringement Support</b>
193-1a	1. A method for conducting an autocatalytic reaction in plugs in a microfluidic system, comprising the steps of:	<p>10X's GemCode platform uses "a method for conducting an autocatalytic reaction in plugs in a microfluidic system."</p> <ul style="list-style-type: none"> <li>• The microfluidic system is 10X's GemCode Instrument or Chromium Controller instrument.</li> <li>• The "plugs" are the microfluidic droplets that are formed in 10X's GemCode Instrument or Chromium Controller instrument.</li> <li>• The autocatalytic reaction is the DNA amplification reaction that is carried out in the droplets.</li> </ul> <p><b><u>10X's GemCode Platform is a microfluidic system using "plugs," which 10X refers to as "droplets" or "GEMs"</u></b></p> <ul style="list-style-type: none"> <li>• The '193 patent's description of "plugs" includes the following: "Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 12 ['193 patent] at 9:27-30.</li> <li>• On August 5, 2015, Michael Schnall-Levin, 10X's Vice President of Computational Biology and Applications, presented a webinar "about the GemCode platform." Ex. 4 [10X Webinar] at 3:17-3:23; <i>see also id.</i> at 3:35-38 ("I'm really excited today to take you through our Platform."). During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the manner described by the '193 patent with reference to the below figure: "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in</li> </ul>

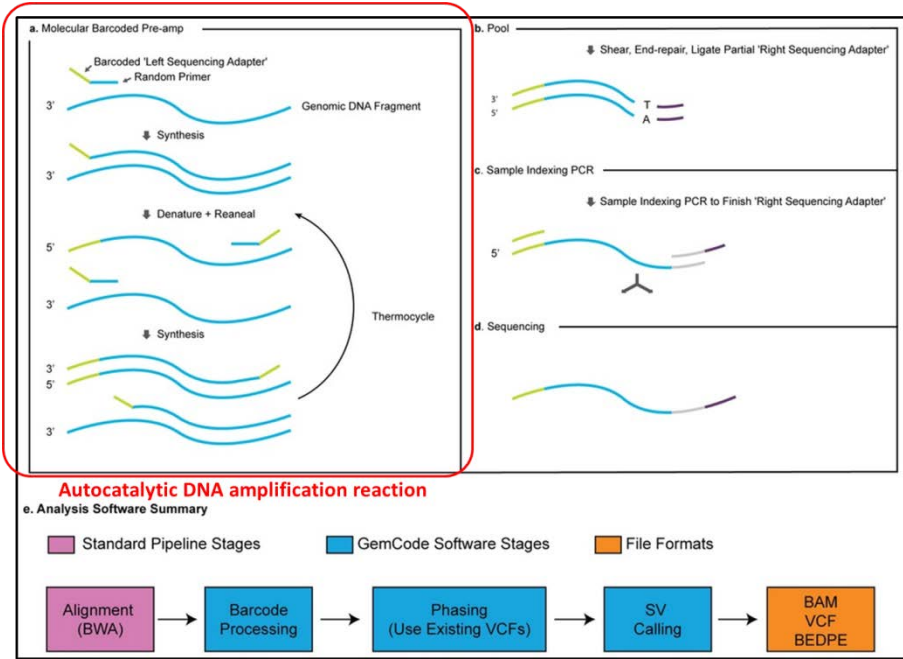
<sup>1</sup> The figures in this chart have been modified to include red annotations that more clearly identify the individual claim elements.



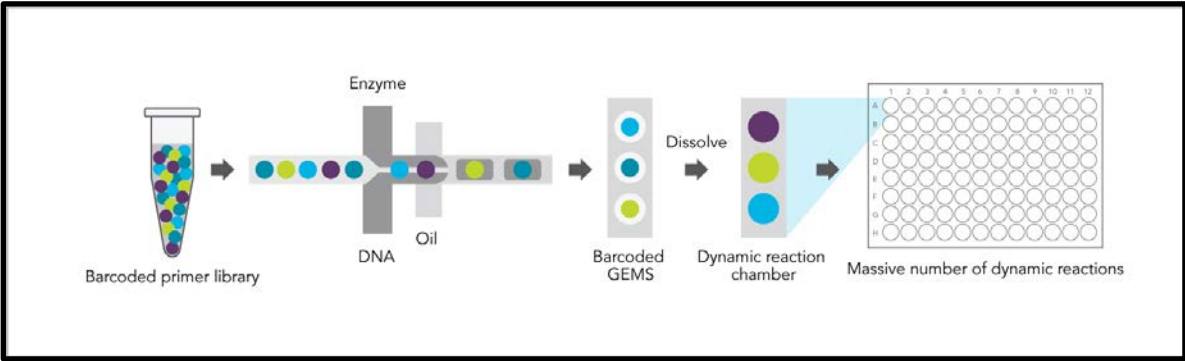
	'193 Claim Language	Infringement Support
		<p>the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <b><i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i></b> Ex. 4 [10X Webinar] at 9:48-10:39.</p> <div data-bbox="720 516 1631 1205"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div> <ul style="list-style-type: none"> <li>10x's website is consistent with Dr. Schnall-Levin's description of 10X's Platform. 10X's website states that "[t]he instrument features precise <i>microfluidics</i> coupled with single button, user-friendly operation." Ex. 39 [10X Website Excerpts] at 3. The website further states that the 10X chip kit "[c]ontains the <i>microfluidic chips</i> and accessories required for sample partitioning." <i>Id.</i> at 5.</li> </ul>

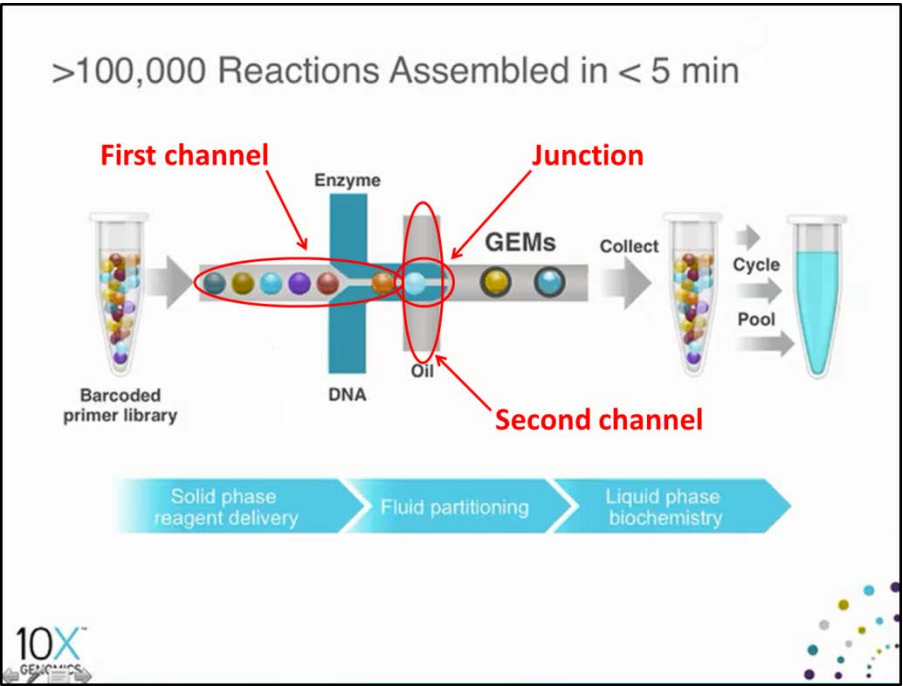
	'193 Claim Language	Infringement Support
		<div data-bbox="716 334 1814 667"> </div> <p data-bbox="716 716 814 748"><i>Id.</i> at 1.</p> <ul data-bbox="674 792 1902 935" style="list-style-type: none"> <li>• 10x Technologies' 2015 presentation at the JP Morgan healthcare conference further shows a microfluidic system for conducting reactions in plugs, including not just a schematic, but a micrograph of the actual microfluidic device. In the micrograph, the plugs are the light gray circles in the right most channel.</li> </ul>

	'193 Claim Language	Infringement Support
		<div data-bbox="718 297 1623 846" data-label="Image"> </div> <p data-bbox="718 885 1203 917">Ex. 37 [JP Morgan Presentation] at 2.</p> <p data-bbox="625 958 1833 1031"><b><u>10X's GemCode platform conducts autocatalytic DNA amplification reactions within the microfluidic droplets ("plugs")</u></b></p> <ul data-bbox="674 1068 1908 1398" style="list-style-type: none"> <li data-bbox="674 1068 1908 1177">• The slide above from 10X's August 2015 presentation is entitled "&gt;100,000 <i>Reactions</i> Assembled in &lt;5 min," which demonstrates that reactions are occurring within the microfluidic droplets.</li> <li data-bbox="674 1218 1908 1398">• The DNA amplification reaction that takes place in 10X's product is an autocatalytic reaction. An autocatalytic reaction is a reaction in which the product of the reaction is also a reactant for the same reaction. The autocatalytic DNA amplification which take place within the microfluidic droplets is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp," which is taken from 10X's recent article in <i>Nature</i></li> </ul>

	'193 Claim Language	Infringement Support
		<p><i>Biotechnology</i> that presents data based on the use of 10X's platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process. As the panel shows, the product of the first synthesis reaction is used as a reactant for another round of DNA synthesis. Hence, the reaction is autocatalytic.</p>  <p>The diagram illustrates the 10X Genomics sequencing process. Panel (a) shows the 'Molecular Barcoded Pre-amp' step, where a 'Barcoded Left Sequencing Adapter' and a 'Random Primer' are used to synthesize a double-stranded DNA fragment from a 'Genomic DNA Fragment'. This is followed by a 'Thermocycle' step, which involves 'Denature + Reanneal' and 'Synthesis' to create multiple copies of the double-stranded DNA. Panel (b) shows the 'Pool' step, where the DNA is sheared, end-repaired, and ligated with a 'Partial Right Sequencing Adapter'. Panel (c) shows the 'Sample Indexing PCR' step, where the DNA is amplified with the 'Right Sequencing Adapter'. Panel (d) shows the 'Sequencing' step, where the DNA is sequenced. Panel (e) shows the 'Analysis Software Summary', which includes a flowchart of the analysis pipeline: Alignment (BWA) → Barcode Processing → Phasing (Use Existing VCFs) → SV Calling → BAM VCF BEDPE. The legend indicates that Standard Pipeline Stages are in pink, GemCode Software Stages are in blue, and File Formats are in orange.</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <i>amplify the DNA</i> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the autocatalytic DNA</li> </ul>

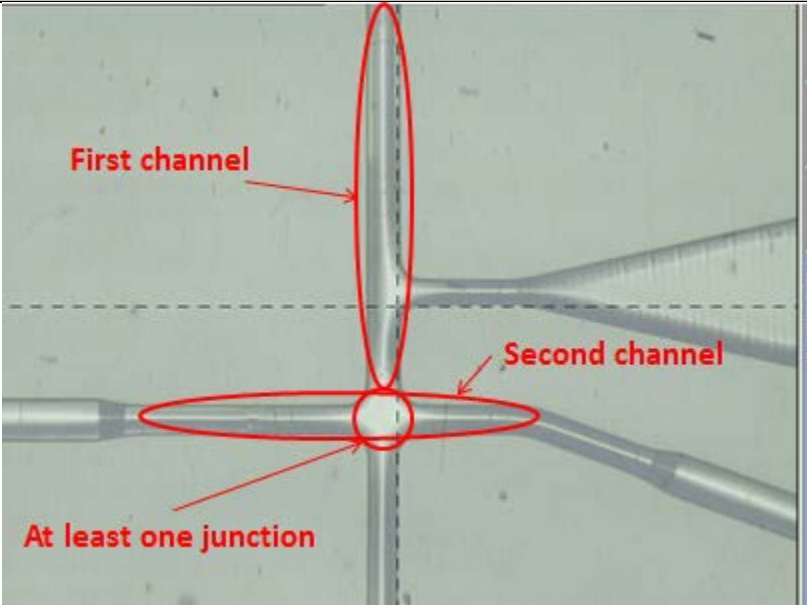
	'193 Claim Language	Infringement Support
		<p>amplification reaction that takes place in the droplets with reference to the figure below. “So now the biochemistry that’s happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you’ve broken the droplets and put everything back together in bulk. First you can concentrate on the top panel showing the biochemistry that’s happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> <div data-bbox="722 735 1623 1408"> <p>Low-input Molecular Barcoding in GEMs</p> <p><b>Autocatalytic DNA amplification reaction</b></p> <p>1 Molecular barcoding in GEMs</p> <p>2 Pool, Ligate right adapter Shear, End-repair, A-tail, Ligate</p> <p>3 Sample Indexing PCR</p> <p>4 Sequence and Analyze</p> <p>10X GENOMICS</p> </div>

	'193 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>The figure below from 10x's website depicts the microfluidic system wherein plugs are received in a "dynamic reaction chamber" wherein a "massive number of dynamic reactions" occur.</li> </ul>  <p>Ex. 37 [10X Website Excerpts] at 1.</p>
193-1b	providing the microfluidic system comprising at least two channels having at least one junction;	<p>10X's GemCode platform provides "the microfluidic system comprising at least two channels having at least one junction."</p> <ul style="list-style-type: none"> <li>The first channel is the central channel where (1) the aqueous fluid containing the target DNA, (2) the aqueous fluid containing the enzyme and other reagents, and (3) the aqueous fluid containing the gel beads combine.</li> <li>The second channel is the channel through which the oil is introduced.</li> <li>The junction is where the central channel and the oil channel intersect.</li> </ul> <p><b><u>10X's GemCode platform uses a microfluidic chip with at least a first channel that intersects a second channel.</u></b></p> <ul style="list-style-type: none"> <li>During his August webinar, Dr. Schnall-Levin explained that the picture below is "a cross-</li> </ul>

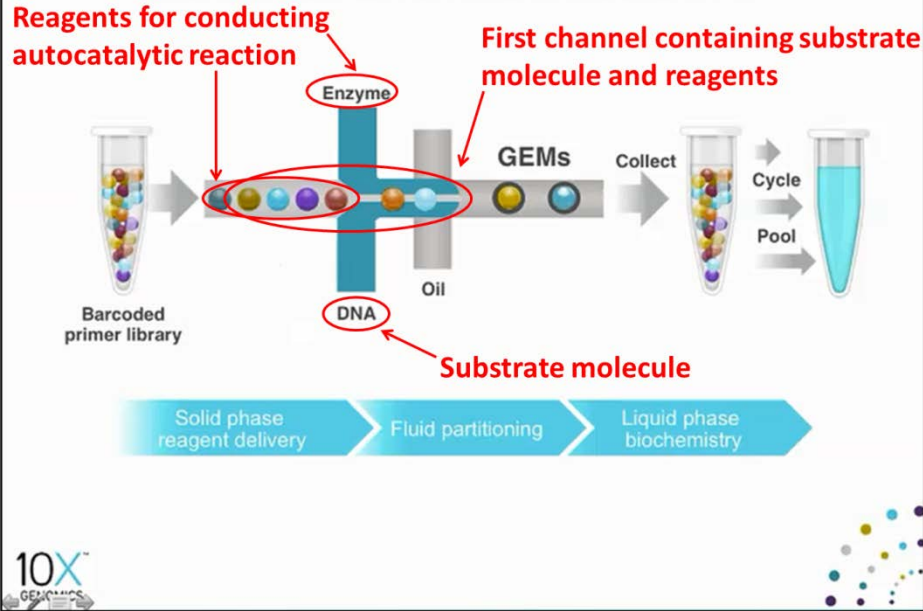
	'193 Claim Language	Infringement Support
		<p>section of one of the <i>channel in our microfluidic chip.</i>” <i>Id.</i> at 9:33-39. “If you look starting from left to right what you see is the channels that are from <i>three different input wells</i>. On the <i>first input well</i> the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the <i>second input well</i> the user mixes our biochemical reagents with their DNA. And on the <i>third input well</i> the user puts in the oil provided again by 10X. <i>There’s a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil</i> which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead” <i>Id.</i> at 9:48-10:39.</p> 



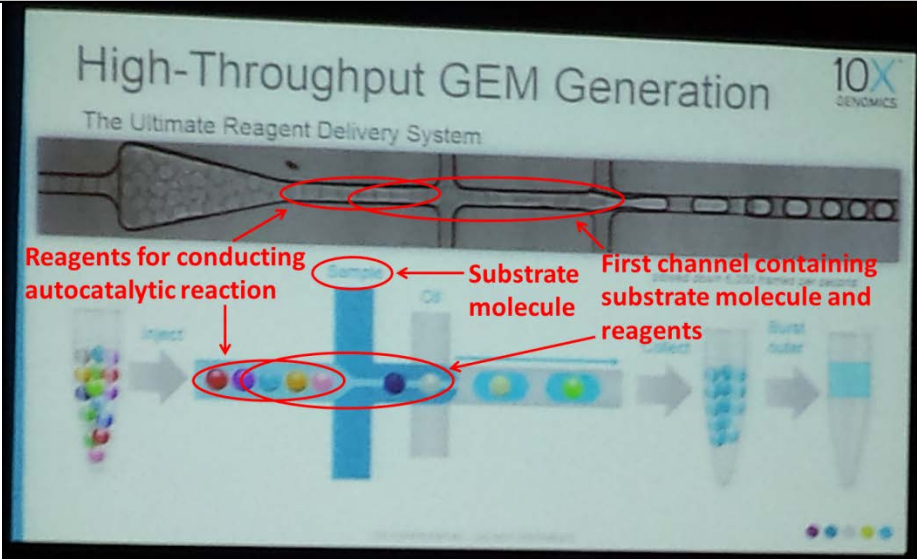
	'193 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>10x's website is consistent with Dr. Schnall-Levin's description of 10X's Platform. 10X's website states that "[t]he instrument features precise <b>microfluidics</b> coupled with single button, user-friendly operation." Ex. 39 [10X Website Excerpts] at 3. The website further states that the 10X chip kit "[c]ontains the <b>microfluidic chips</b> and accessories required for sample partitioning." <i>Id.</i> at 5. The figure below from 10x's website depicts the microfluidic system with at least two channels having at least one junction.</li> </ul> <div data-bbox="722 557 1818 886"> <p>The diagram illustrates a microfluidic process. On the left, a test tube labeled 'Barcoded primer library' feeds into a 'First channel'. This channel contains 'Enzyme' and 'DNA'. A 'Second channel' containing 'Oil' joins the first at a 'Junction'. The mixture then flows into a 'Barcoded GEMS' stage, followed by a 'Dissolve' step into a 'Dynamic reaction chamber'. The final output is a grid labeled 'Massive number of dynamic reactions'.</p> </div> <p><i>Id.</i> at 1.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below.</li> </ul>

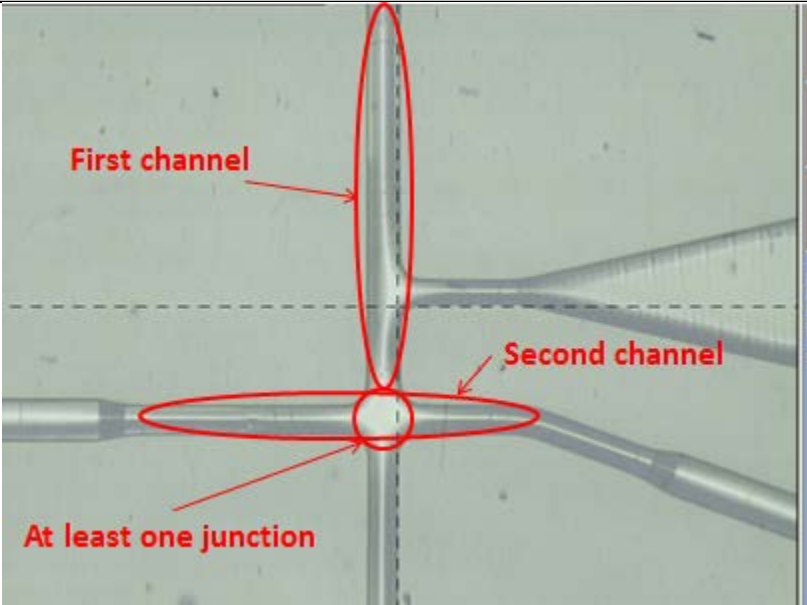
	'193 Claim Language	Infringement Support
		
193-1c	<p>flowing an aqueous fluid containing at least one substrate molecule and reagents for conducting an autocatalytic reaction through a first channel of the at least two channels;</p>	<p>10X's GemCode platform "flow[s] an aqueous fluid containing at least one substrate molecule and reagents for conducting an autocatalytic reaction through a first channel of the at least two channels."</p> <ul style="list-style-type: none"> <li>• The aqueous fluid containing at least one substrate molecule and reagents for conducting an autocatalytic reaction is the combination of (1) the aqueous fluid that contains the user's sample DNA, (2) the aqueous fluid that contains 10X's barcoded gel beads, and (3) the aqueous fluid that contains enzymes and reagents that react with the DNA.</li> <li>• These three fluids combine at a first junction to yield a combined fluid that has substrate DNA and reagents, including at least primers and nucleotides. The primers are delivered via the gel beads.</li> <li>• The autocatalytic reaction that takes place is the amplification of DNA in the droplets.</li> <li>• The first channel is the central channel that perpendicularly intersects the oil channel.</li> </ul>

	'193 Claim Language	Infringement Support
		<p><b><u>10X's GemCode platform uses an aqueous fluid containing at least one substrate molecule (DNA) and at least one biochemical reagent (nucleotides and primers) that flows through a first channel of the microfluidic chip</u></b></p> <ul style="list-style-type: none"> <li>• The '193 patent states that "Suitable reactants for use in the invention include synthetic small molecules, biological molecules (i.e., proteins, DNA, RNA, carbohydrates, sugars, etc.), metals and metal ions, and the like." Ex. 12 ['193 patent] at 20:10-13. Thus, in the '193 patent, "DNA" is a type of "substrate molecule."</li> <li>• During his August 5, 2015 presentation, Dr. Schnall-Levin explained that the picture below is "a cross-section of one of the channels in our microfluidic chip." Ex. 4 [10X Webinar] at 9:33-39. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10x. <i>On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" <i>Id.</i> at 9:48-10:39. Thus, the aqueous solution of the gel beads, biochemical reagents and DNA ("substrate molecule") flow through a first channel.</li> </ul>

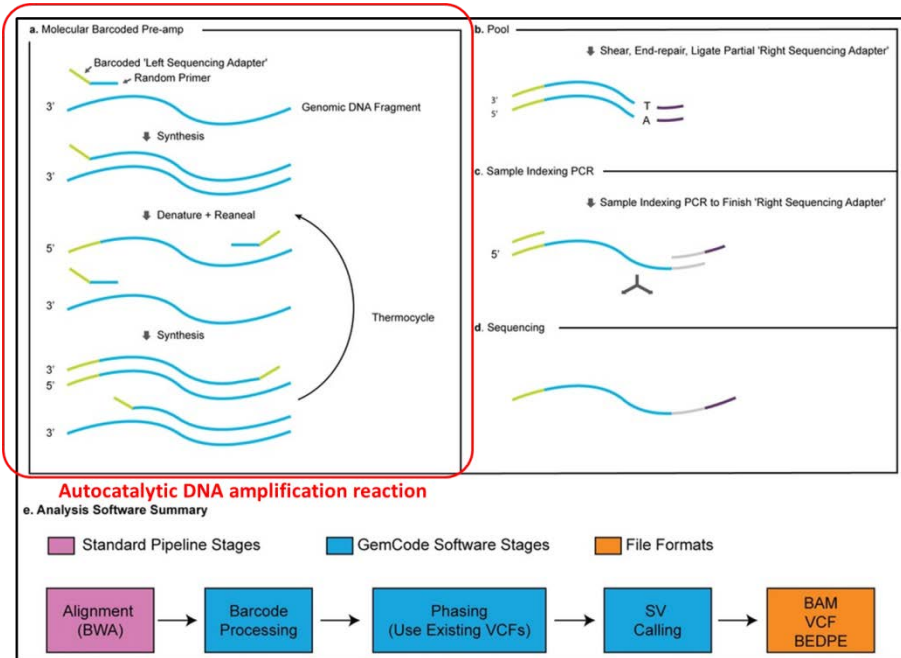
	'193 Claim Language	Infringement Support
		<p data-bbox="787 349 1495 386">&gt;100,000 Reactions Assembled in &lt; 5 min</p>  <ul data-bbox="674 1036 1885 1253" style="list-style-type: none"> <li>• In the figure above, the aqueous solutions of DNA and enzyme are shown in blue flowing through a first channel.</li> <li>• The figure below from 10x's website further notes the introduction of DNA for sequencing and enzyme through a continuously flowing aqueous solution through a central channel. It further shows a reaction taking place in a "Dynamic reaction chamber."</li> </ul>

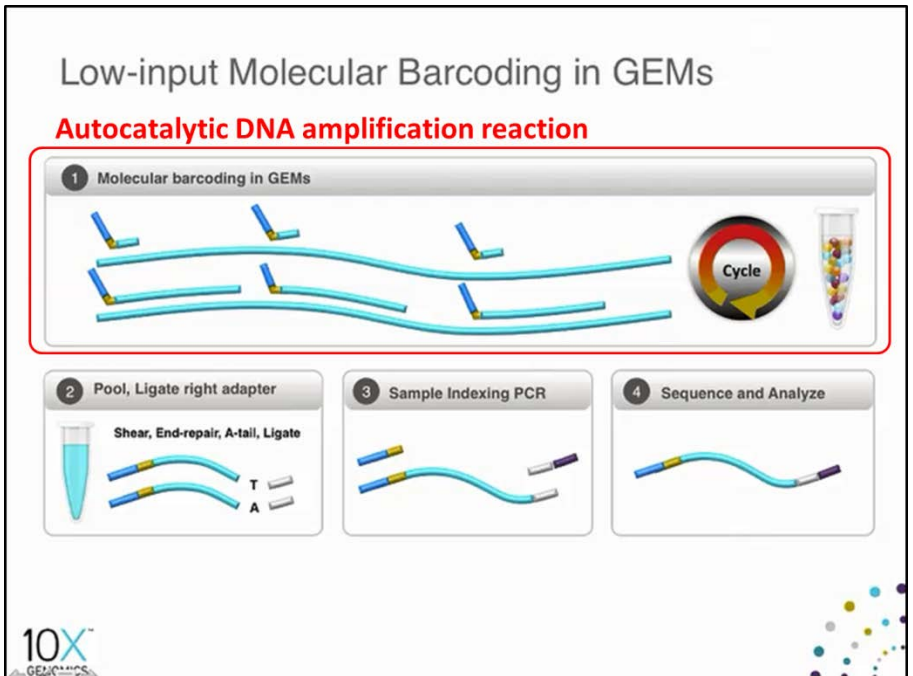
	'193 Claim Language	Infringement Support
		<div data-bbox="726 305 1854 638"> <p>The diagram illustrates a microfluidic workflow. It begins with a 'Barcoded primer library' (represented by a vial of colored beads) which is combined with 'Enzyme' and 'DNA' in a 'First channel containing substrate molecule and reagents'. This mixture is then 'Dissolved' into a 'Dynamic reaction chamber' where a 'Substrate molecule' is added. The final output is a 'Massive number of dynamic reactions' shown in a 96-well plate format.</p> </div> <p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which an aqueous fluid (shown in blue) flows and that contains a molecule (labeled as "sample") and at least one other reagent (e.g., nucleotides) for subsequent use in a DNA amplification reaction.</li> </ul>

	'193 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan Presentation] at 2.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. The aqueous fluid containing the sample DNA ("substrate molecule") and enzyme/reagents flow through the channel labeled "first channel."</li> </ul>

	'193 Claim Language	Infringement Support
		 <p><b><u>The at least one biochemical reagent (nucleotides and primers) in the aqueous fluid is for conducting an autocatalytic reaction with the substrate molecule (DNA).</u></b></p> <ul style="list-style-type: none"> <li>The DNA amplification reaction that takes place in 10X's GemCode platform is an autocatalytic reaction. An autocatalytic reaction is a reaction in which the product of the reaction is also a reactant for the same reaction. The autocatalytic DNA amplification which take place within the microfluidic droplets is depicted in the figure below in the panel labeled "a. Molecular Barcoded Pre-amp," which is taken from 10X's recent article in <i>Nature Biotechnology</i> that presents data based on the use of 10X's platform. The figure below shows a single stranded "Genomic DNA Fragment" that is extended through the use of a "Random Primer." The resulting double-stranded DNA fragment is then denatured, and the process is repeated through the thermocycling process. As the panel shows, the product of the first synthesis reaction is used as a reactant for another round of DNA synthesis.</li> </ul>

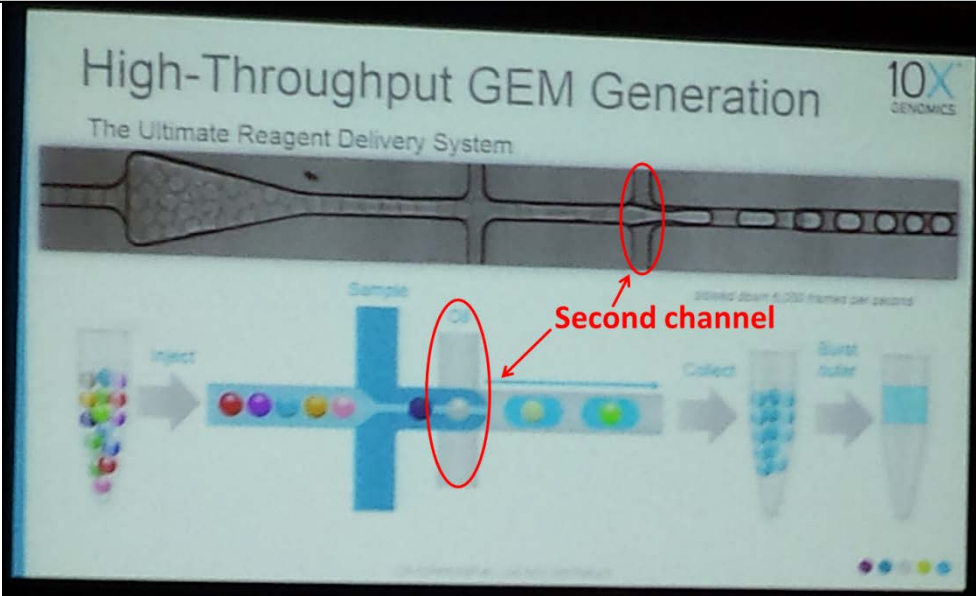


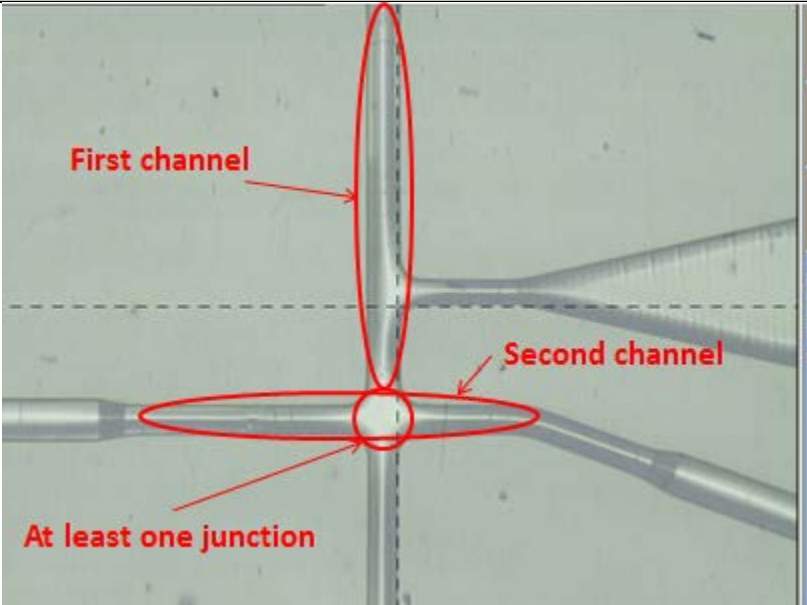
	'193 Claim Language	Infringement Support
		<p>Hence, the reaction is autocatalytic. To carry out this reaction, the droplets include at least primers and nucleotides as reagents.</p>  <p>The diagram illustrates the GemCode sequencing process, which is an autocatalytic DNA amplification reaction. It is divided into several stages:</p> <ul style="list-style-type: none"> <li><b>a. Molecular Barcoded Pre-amp:</b> This stage shows a genomic DNA fragment being amplified using a barcoded left sequencing adapter and a random primer. The process involves synthesis, denature + reanneal, and another round of synthesis, all occurring within a thermocycle.</li> <li><b>b. Pool:</b> This stage shows the pooling of the amplified DNA fragments, followed by shearing, end-repair, and ligation of a partial right sequencing adapter.</li> <li><b>c. Sample Indexing PCR:</b> This stage shows the sample indexing PCR, which is used to finish the right sequencing adapter.</li> <li><b>d. Sequencing:</b> This stage shows the final sequencing of the DNA fragments.</li> <li><b>e. Analysis Software Summary:</b> This stage shows the analysis pipeline, which includes Alignment (BWA), Barcode Processing, Phasing (Use Existing VCFs), SV Calling, and the final output in BAM, VCF, BED, and PE formats.</li> </ul> <p>The diagram is titled "Autocatalytic DNA amplification reaction" and highlights the process as being autocatalytic.</p> <p>Ex. 5 [<i>Nature Biotechnology</i>] at Supp. Fig. 1. As 10X's publication states, "1 ng of sample DNA was used for GEM reactions where DNA molecules were partitioned into droplets to <i>amplify the DNA</i> and introduce 14-bp partition barcodes." <i>Id.</i> at 3432.</p> <ul style="list-style-type: none"> <li>During his August 2015 webinar, Dr. Schall-Levin also described the autocatalytic DNA amplification reaction that takes place in the droplets with reference to the figure below. "So now the biochemistry that's happening as part of the process. The biochemistry is divided into two major stages. The first happens inside of the droplets and the second happens after you've broken the droplets and put everything back together in bulk. First you</li> </ul>

	'193 Claim Language	Infringement Support
		<p>can concentrate on the top panel showing the biochemistry that's happening inside the droplets. The droplets after coming off the instrument are placed in a standard 96-well plate and put on a thermal cycler for a thermal cycling protocol. <b><i>During this thermal cycling protocol, oligos which have been released as the gel bead fall apart prime off of the genome and do a low-level of copying.</i></b> The result is that you form molecules which contain one-half of the Illumina sequencing machinery containing the 10X barcode and a copy of the genomic template.” Ex. 4 [10X Webinar] at 13:00-53.</p> 
193-1d	flowing an oil through the second channel of the at least	<p>10X's GemCode platform “flow[s] an oil through the second channel of the at least two channels.”</p> <ul style="list-style-type: none"> <li>The second channel is the oil channel that perpendicularly intersects the central channel.</li> </ul>

	'193 Claim Language	Infringement Support
	two channels;	<p><b><u>10X's GemCode platform continuously flows an oil through a second channel that intersects at a cross with a first channel containing an aqueous fluid.</u></b></p> <ul style="list-style-type: none"> <li>Dr. Schnall-Levin explained that in the below picture, "<i>on the third input well the user puts in the oil provided again by 10X</i>". There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead</i>" Id. at 9:48-10:39. Thus, the channel containing the oil intersects and flows into the channel containing the aqueous solution of the gel beads, biochemical reagents and DNA.</li> </ul> <div data-bbox="730 703 1619 1377"> <p>&gt;100,000 Reactions Assembled in &lt; 5 min</p> </div>

	'193 Claim Language	Infringement Support
		<ul style="list-style-type: none"> <li>• In the figure above the channel containing the continuously flowing oil is shown in grey.</li> <li>• The figure below from 10x's website further notes the continuously flowing oil from a second channel shown in light grey.</li> </ul> <div data-bbox="722 483 1808 812"> <p style="color: red; text-align: center;"><b>Second channel</b></p> </div> <p>Ex. 39 [10X Website Excerpts] at 1.</p> <ul style="list-style-type: none"> <li>• Similarly, 10X's 2015 JP Morgan presentation shows a microfluidic system through which an aqueous fluid (shown in blue) flows and that contains a molecule (labeled as "sample") and at least one other reagent (e.g., nucleotides) for subsequent use in a DNA amplification reaction. The oil is shown in a second channel in light grey:</li> </ul>

	'193 Claim Language	Infringement Support
		 <p>Ex. 37 [JP Morgan Presentation] at 2.</p> <ul style="list-style-type: none"> <li>10X's GemCode platform comprises eight microfluidic systems arranged in parallel. Below is a recent image of one such microfluidic system from 10X's product. The geometry of the microfluidic system shown in this image is a variation of the arrangement depicted in the other figures in this chart. This arrangement functions in the same manner as the other arrangements depicted in this chart, except that the enzyme/reagents and sample DNA are delivered via the same inlet. This alternate arrangement of microfluidic channels still meets all elements of the claims, as shown in the annotated image below. The oil flows through the channel labeled "second channel."</li> </ul>

	'193 Claim Language	Infringement Support
		 <p>The image is a micrograph showing a microfluidic device with two channels intersecting at a central junction. A red oval highlights the junction area, with a red arrow pointing to it and the text 'At least one junction'. Another red oval highlights one of the channels, with a red arrow pointing to it and the text 'First channel'. A third red oval highlights the other channel, with a red arrow pointing to it and the text 'Second channel'.</p>
193-1e	<p>forming at least one plug of the aqueous fluid containing the at least one substrate molecule and reagents by partitioning the aqueous fluid with the flowing oil at the junction of the at least two channels, the plug being substantially surrounded by an oil</p>	<p>10X's GemCode platform forms "at least one plug of the aqueous fluid containing the at least one substrate molecule and reagents by partitioning the aqueous fluid with the flowing oil at the junction of the at least two channels, the plug being substantially surrounded by an oil flowing through the channel, wherein the at least one plug comprises at least one substrate molecule and reagents for conducting an autocatalytic reaction with the at least one substrate molecule."</p> <ul style="list-style-type: none"> <li>• The "plugs" are the microfluidic droplets that are formed at the junction between the oil and the aqueous fluid containing the substrate molecule and reagents.</li> <li>• The substrate molecule is the user's sample DNA</li> <li>• The reagents are nucleotides and primers (which are delivered via the gel beads) that are used in an autocatalytic DNA amplification reaction with the substrate DNA.</li> </ul> <p><b><u>10X's GemCode platform forms microfluidic droplets ("plugs") by partitioning an aqueous</u></b></p>

	'193 Claim Language	Infringement Support
	<p>flowing through the channel, wherein the at least one plug comprises at least one substrate molecule and reagents for conducting an autocatalytic reaction with the at least one substrate molecule; and</p>	<p><b><u>fluid flowing through a first channel with an oil flowing through a second channel such that the plugs are substantially surrounded by the oil.</u></b></p> <ul style="list-style-type: none"> <li>• The '193 patent's description of "plugs" includes the following: "'Plugs' in accordance with the present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 12 ['193 patent] at 9:27-30.</li> <li>• During his August 2015 presentation, Dr. Schnall-Levin described how 10X's microfluidic device forms plugs in the same manner as the '193 patent. The process is depicted in the figure below. "If you look starting from left to right what you see is the channels that are from three different input wells. On the first input well the user puts in the barcoded gel beads. This is a reagent delivered by 10X. On the second input well the user mixes our biochemical reagents with their DNA. And on the third input well the user puts in the oil provided again by 10X. There's a flow from left to right and the gel beads first flow through the mix of biochemical reagents and DNA mixing with them uniformly. <i>They then flow through a second cross of oil which pinches off droplets each of which contain a small portion of the DNA from the user and a gel bead.</i>" Ex. 4 [10X Webinar] at 9:48-10:39.</li> </ul>